10/29/04

Connecting via Winsock to STN

Welcome to STN International! Enter x:x

LOGINID:ssspta1612rxd

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS 1		Web Page URLs for STN Seminar Schedule - N. America
NEWS 2		"Ask CAS" for self-help around the clock
NEWS 3	JUL 12	BEILSTEIN enhanced with new display and select options, resulting in a closer connection to BABS
NEWS 4	AUG 02	IFIPAT/IFIUDB/IFICDB reloaded with new search and display fields
NEWS 5	AUG 02	CAplus and CA patent records enhanced with European and Japan Patent Office Classifications
NEWS 6	AUG 02	The Analysis Edition of STN Express with Discover! (Version 7.01 for Windows) now available
NEWS 7	AUG 27	BIOCOMMERCE: Changes and enhancements to content coverage
NEWS 8	AUG 27	BIOTECHABS/BIOTECHDS: Two new display fields added for legal status data from INPADOC
NEWS 9	SEP 01	INPADOC: New family current-awareness alert (SDI) available
NEWS 10	SEP 01	New pricing for the Save Answers for SciFinder Wizard within STN Express with Discover!
NEWS 11	SEP 01	New display format, HITSTR, available in WPIDS/WPINDEX/WPIX
NEWS 12	SEP 27	STANDARDS will no longer be available on STN
NEWS 13	SEP 27	SWETSCAN will no longer be available on STN
NEWS 14	OCT 28	KOREAPAT now available on STN

NEWS EXPRESS	OCTOBER 29 CURRENT WINDOWS VERSION IS V7.01A, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 11 AUGUST 2004
NEWS HOURS	STN Operating Hours Plus Help Desk Availability
NEWS INTER	General Internet Information
NEWS LOGIN	Welcome Banner and News Items
NEWS PHONE	Direct Dial and Telecommunication Network Access to STN
NEWS WWW	CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that specific topic.

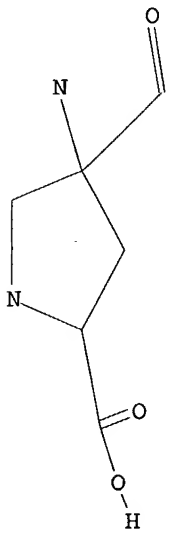
All use of STN is subject to the provisions of the STN Customer agreement. Please note that this agreement limits use to scientific research. Use for software development or design or implementation of commercial gateways or other similar uses is prohibited and may result in loss of user privileges and other penalties.

* * * * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 16:46:25 ON 29 OCT 2004

10/29/04

```
=> file registry
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.21       0.21

FILE 'REGISTRY' ENTERED AT 16:46:34 ON 29 OCT 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2004 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   27 OCT 2004  HIGHEST RN 770693-70-4
DICTIONARY FILE UPDATES:  27 OCT 2004  HIGHEST RN 770693-70-4

TSCA INFORMATION NOW CURRENT THROUGH MAY 21, 2004

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=>
Uploading C:\Stnexp4 corrupted\QUERIES\10613961.str

L1      STRUCTURE UPLOADED

=> d l1
L1 HAS NO ANSWERS
L1              STR
```



Structure attributes must be viewed using STN Express query preparation.

10/29/04

```
=> s l1
SAMPLE SEARCH INITIATED 16:46:50 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -     11 TO ITERATE

100.0% PROCESSED      11 ITERATIONS                                  6 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:           22 TO      418
PROJECTED ANSWERS:               6 TO      266

L2            6 SEA SSS SAM L1

=> s l1 ful
FULL SEARCH INITIATED 16:46:57 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -    238 TO ITERATE

100.0% PROCESSED     238 ITERATIONS                                 88 ANSWERS
SEARCH TIME: 00.00.01

L3           88 SEA SSS FUL L1

=> file caplus
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                   155.42     155.63

FILE 'CAPLUS' ENTERED AT 16:47:00 ON 29 OCT 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)


Copyright of the articles to which records in this database refer is
held by the publishers listed in the PUBLISHER (PB) field (available
for records published or updated in Chemical Abstracts after December
26, 1996), unless otherwise indicated in the original publications.
The CA Lexicon is the copyrighted intellectual property of the
American Chemical Society and is provided to assist you in searching
databases on STN.  Any dissemination, distribution, copying, or storing
of this information, without the prior written consent of CAS, is
strictly prohibited.

FILE COVERS 1907 - 29 Oct 2004  VOL 141 ISS 19
FILE LAST UPDATED: 28 Oct 2004  (20041028/ED)

  This file contains CAS Registry Numbers for easy and accurate
  substance identification.


=> s l3
L4           51 L3

=> d  abs bib fhitstr 1-51

L4   ANSWER 1 OF 51  CAPLUS  COPYRIGHT 2004 ACS on STN
```

AB Glutamate carboxypeptidase II (GCP II) inhibition has previously been shown to be protective against long-term neuropathy in diabetic animals. In the current study, the authors have determined that the GCP II inhibitor 2-(phosphonomethyl) pentanedioic acid (2-PMPA) is protective against glucose-induced programmed cell death (PCD) and neurite degeneration in dorsal root ganglion (DRG) neurons in a cell culture model of diabetic neuropathy. In this model, inhibition of caspase activation is mediated through the group II metabotropic glutamate receptor, mGluR3. 2-PMPA neuroprotection is completely reversed by the mGluR3 antagonist (S)-α-ethylglutamic acid (EGLU). In contrast, group I and III mGluR inhibitors have no effect on 2-PMPA neuroprotection. Furthermore, the authors show that two mGluR3 agonists, the direct agonist (2R,4R)-4-aminopyrrolidine-2, 4-dicarboxylate (APDC) and N-acetyl-aspartyl-glutamate (NAAG) provide protection to neurons exposed to high glucose conditions, consistent with the concept that 2-PMPA neuroprotection is mediated by increased NAAG activity. Inhibition of GCP II or mGluR3 may represent a novel mechanism to treat neuronal degeneration under high-glucose conditions.

AN 2004:302637 CAPLUS

DN 140:369191

TI Protection against glucose-induced neuronal death by NAAG and GCP II inhibition is regulated by mGluR3

AU Berent-Spillson, Alison; Robinson, Amanda M.; Golovoy, David; Slusher, Barbara; Rojas, Camilo; Russell, James W.

CS University of Michigan Neuroscience Program, University of Michigan Department of Neurology, Ann Arbor, MI, 48109-0588, USA

SO Journal of Neurochemistry (2004), 89(1), 90-99
CODEN: JONRA9; ISSN: 0022-3042

PB Blackwell Publishing Ltd.

DT Journal

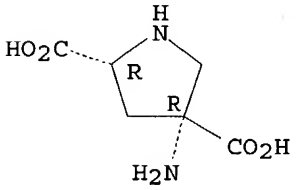
LA English

IT **169209-63-6**
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(protection against glucose-induced neuronal death by NAAG and GCP II inhibition is regulated by mGluR3 in rat neuronal cell culture model of diabetic neuropathy)

RN 169209-63-6 CAPLUS

CN 2,4-Pyrrolidinedicarboxylic acid, 4-amino-, (2R,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RE.CNT 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

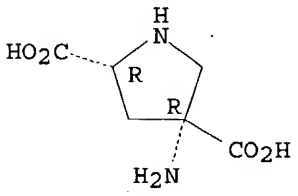
L4 ANSWER 2 OF 51 CAPLUS COPYRIGHT 2004 ACS on STN

AB Carbon monoxide has been shown to act as a neurotransmitter and neuronal messenger in the brain. Heme oxygenase catalyzes the conversion of heme to carbon monoxide and biliverdin. We have recently reported that carbon

monoxide was involved in central cardiovascular regulation. Carbon monoxide modulated the baroreflex and may affect glutamatergic neurotransmission. In addition, metabotropic glutamate receptors may be coupled to the activation of heme oxygenase in the nucleus tractus solitarii of rats. The present study was designed to investigate the possible interactions of carbon monoxide and metabotropic glutamate receptor groups in the nucleus tractus solitarii. Unilateral microinjection of several agonists for metabotropic glutamate receptor groups such as (R,S)-3,5-dihydroxyphenylglycine (DHPG) (group I) (0.03 nmol), 2R,4R-4-aminopyrrolidine-2,4-dicarboxylate (APDC) (group II) (0.3 nmol), and L-(+)-2-amino-4-phosphonobutyric acid (L-AP4) (group III) (0.3 nmol) produced a significant decrease in blood pressure and heart rate. Among the metabotropic glutamate receptor agonists, prior administration of zinc protoporphyrin IX, an inhibitor of heme oxygenase activity, significantly attenuated the cardiovascular effects of APDC and L-AP4, and failed to attenuate the cardiovascular responses of DHPG. These results indicated interactions between carbon monoxide and group II and III metabotropic glutamate receptors in central cardiovascular regulation.

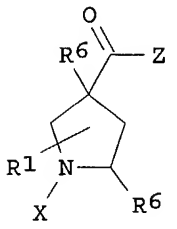
AN 2004:181499 CAPLUS
DN 140:314933
TI Interactions of carbon monoxide and metabotropic glutamate receptor groups in the nucleus tractus solitarii of rats
AU Lin, Chia-Hui; Lo, Wan-Chen; Hsiao, Michael; Tung, Che-Se; Tseng, Ching-Jiunn
CS Department of Medical Education and Research, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan
SO Journal of Pharmacology and Experimental Therapeutics (2004), 308(3), 1213-1218
CODEN: JPETAB; ISSN: 0022-3565
PB American Society for Pharmacology and Experimental Therapeutics
DT Journal
LA English
IT **169209-63-6**
RL: PAC (Pharmacological activity); BIOL (Biological study)
(interactions of carbon monoxide and metabotropic glutamate receptor groups and cardiovascular regulation in nucleus tractus solitarii)
RN 169209-63-6 CAPLUS
CN 2,4-Pyrrolidinedicarboxylic acid, 4-amino-, (2R,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

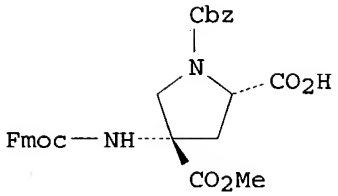


RE.CNT 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

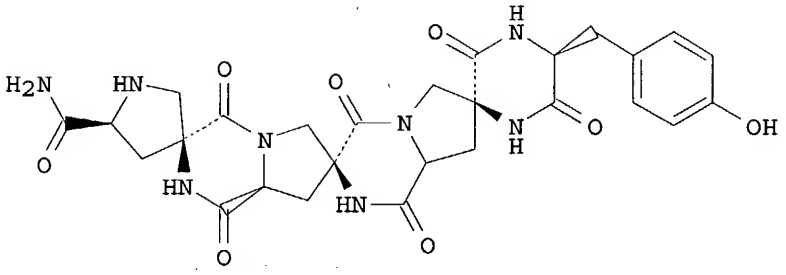
L4 ANSWER 3 OF 51 CAPLUS COPYRIGHT 2004 ACS on STN
GI



I



II



III

AB The invention provides mol. building blocks of rigid bis(amino acids), which can be linked together through the formation of rigid diketopiperazine rings to provide the desired three dimensional structure. The bis(amino acid) building blocks are applied to the synthesis of macromols. Compds. such as I (R1 is H or a functional group; R5 is N3 or NR2Y, where Y is a protecting group and R2 is H or a functional group; R6 is CO2H or a strongly-activated ester; X is a protecting group; Z is a weak leaving group) are claimed. Thus, building block II (Cbz = benzyloxycarbonyl, Fmoc = fluorenylmethoxycarbonyl) was prepared from trans-4-hydroxy-L-proline and applied to the sequential solid-phase synthesis of mol. rod III.

AN 2004:120944 CAPLUS
DN 140:181808

TI Preparation of bis(amino acid) molecular scaffolds

IN Schafmeister, Christian E.
PA University of Pittsburgh of the Commonwealth System of Higher Education, USA

SO PCT Int. Appl., 85 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004013282	A2	20040212	WO 2003-US21399	20030705
	WO 2004013282	A3	20040617		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC,

NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

	US 2004082783	A1	20040429	US 2003-612098	20030702
	US 2004077879	A1	20040422	US 2003-613961	20030705
PRAI	US 2002-401474P	P	20020806		
	US 2003-612098	A	20030702		
	US 2003-613961	A	20030705		

OS MARPAT 140:181808

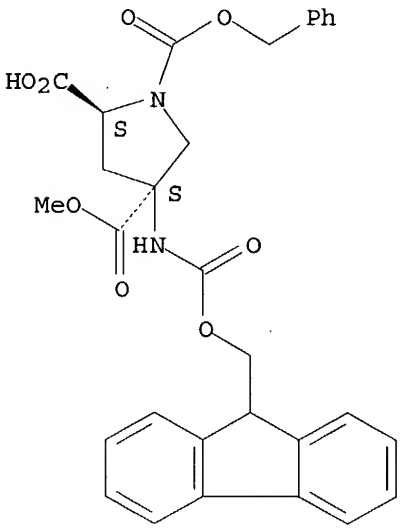
IT **526223-02-9P**

RL: SPN (Synthetic preparation); PREP (Preparation)
(proline bis(amino acid) derivs. in synthesis of piperazinediones)

RN 526223-02-9 CAPLUS

CN 1,2,4-Pyrrolidinetricarboxylic acid, 4-[[(9H-fluoren-9-ylmethoxy)carbonyl]amino]-, 4-methyl 1-(phenylmethyl) ester, (2S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



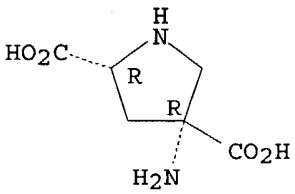
L4 ANSWER 4 OF 51 CAPLUS COPYRIGHT 2004 ACS on STN

AB The objective of the current study was to facilitate functional calcium assays, compatible with the fluorometric imaging plate reader platform, for the human metabotropic glutamate receptor (mGluR) subtypes 2 and 4, by co-expressing each receptor with a G-protein chimera comprising Gαq with the C-terminal five amino acids replaced with those from Gαi3 (GqGi3). Transfection of GqGi3 into previously validated stable CHO cell lines expressing mGluR2 or mGluR4 allowed for the selection of new double transfectants in which application of L-glutamate and other mGluR agonists resulted in calcium coupling with a high signal:noise ratio (maximal changes in relative fluorescence units up to 20,000). The rank order of agonist potency for the stimulation of calcium mobilization in the mGluR2/GqGi3 stable cell line was LY354740>L-CCG-I=DCG-IV>L-glutamate≥(2R,4R)-APDC≥(1S,3R)-ACPD. In the mGluR4/GqGi3 stable cell line the rank order of agonist potency was L-AP4>L-SOP≥ACPT-I=L-CCG-I≥L-glutamate=(R,S)-PPG. By comparison, equivalent potency orders and a significant correlation in functional activities were observed when the same compds. were profiled in [35S]GTPγS binding assays for each mGluR subtype. These results

validate the use of functional calcium assays, amenable to high-throughput applications on the fluorometric imaging plate reader, for the mGluR2 and mGluR4 subtypes when co-expressed in stable cell lines with the GqGi3 chimera.

AN 2003:669206 CAPLUS
DN 139:391600
TI Functional calcium coupling with the human metabotropic glutamate receptor subtypes 2 and 4 by stable co-expression with a calcium pathway facilitating G-protein chimera in Chinese hamster ovary cells
AU Kowal, Dianne; Nawoschik, Stanley; Ochalski, Rafal; Dunlop, John
CS Neuroscience Discovery Research, Wyeth Research, Princeton, NJ, 08543, USA
SO Biochemical Pharmacology (2003), 66(5), 785-790
CODEN: BCPCA6; ISSN: 0006-2952
PB Elsevier Science B.V.
DT Journal
LA English
IT **169209-63-6**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(mGluR2 agonist; functional calcium coupling with human mGluR and mGluR4 by stable co-expression with a calcium pathway facilitating G-protein chimera in Chinese hamster ovary cells)
RN 169209-63-6 CAPLUS
CN 2,4-Pyrrolidinedicarboxylic acid, 4-amino-, (2R,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



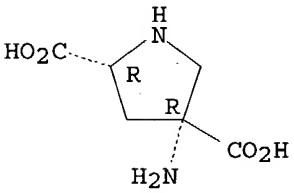
RE.CNT 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 51 CAPLUS COPYRIGHT 2004 ACS on STN
AB Previous investigations have shown that metabotropic glutamate (mGlu) receptors might be involved in the amphetamine-induced motor response. This work studied the involvement of mGlu receptors in the nucleus accumbens (NAcc) in the locomotor-activating properties of amphetamine in rats well habituated to their exptl. environment, a condition known to modulate the motor response to amphetamine. Focal infusion of the group I mGlu receptor antagonist S-4-carboxyphenylglycine, which has no effect on basal motor activity, virtually suppressed the locomotor response to amphetamine, while infusion of the group II mGlu receptor antagonist LY 341495 or the group III mGlu receptor agonist AP4, at the minimal dose that produces locomotor activation, reduced it by approx. half. These effects were blocked by the group I mGlu receptor agonist dihydroxyphenylglycine, the group II mGlu receptor agonist aminopyrrolidinedicarboxylate and the group III mGlu receptor antagonist methylphosphonophenylglycine, resp. These data confirm that mGlu receptors in the NAcc contribute to the psychostimulant motor effect of amphetamine. The results are discussed in the light of recent neuropharmacol. studies that have defined the effects of these mGlu receptor ligands on basal motor activity and dopamine receptor

agonist-induced locomotor responses in rats exposed to similar exptl. procedures. It is suggested that the contribution of mGlu receptors to the amphetamine-induced motor response may result mainly from their interactions (either direct or indirect) with D1-like receptors in the NAcc.

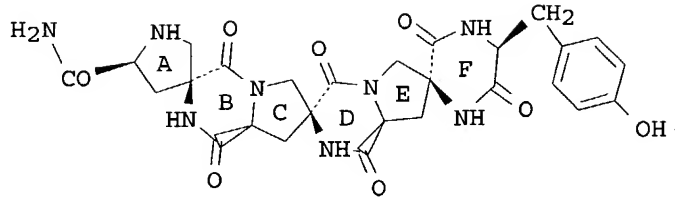
AN 2003:268912 CAPLUS
DN 139:270878
TI Blockade of the locomotor-stimulant effects of amphetamine by group I, group II, and group III metabotropic glutamate receptor ligands in the rat nucleus accumbens: possible interactions with dopamine receptors
AU David, H. N.; Abraini, J. H.
CS Centre CYCERON, UMR CNRS 6551, Universite de Caen Basse-Normandie, Caen, 14074, Fr.
SO Neuropharmacology (2003), 44(6), 717-727
CODEN: NEPHBW; ISSN: 0028-3908
PB Elsevier Science Ltd.
DT Journal
LA English
IT **169209-63-6**
RL: PAC (Pharmacological activity); BIOL (Biological study)
(locomotor-stimulant effects of amphetamine response to the group II metabotropic glutamate receptor agonist aminopyrrolidinedicarboxylic acid in the nucleus accumbens)
RN 169209-63-6 CAPLUS
CN 2,4-Pyrrolidinedicarboxylic acid, 4-amino-, (2R,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

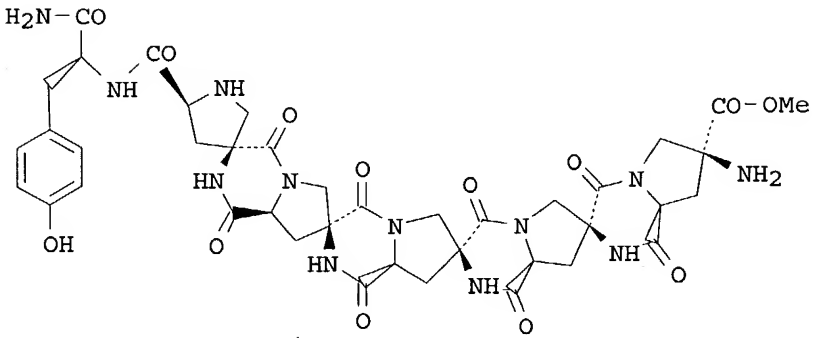


RE.CNT 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 6 OF 51 CAPLUS COPYRIGHT 2004 ACS on STN
GI



I

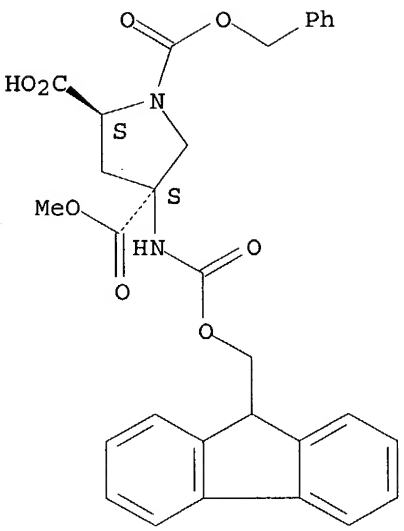


II

AB We report a synthetic approach to spiro-ladder oligomers of defined length and structure that form water-soluble mol. rods. We describe the synthesis of a chiral mol. building block and its assembly on solid support to form flexible chains that were then rigidified by the parallel formation of several diketopiperazine rings. Two mol. rods approx. 15 and 25 Å in length were synthesized containing three and five monomers, resp. (I and II). The mol. rods were easily functionalized on both ends and were shown to have high water solubility, making them compatible with biol. buffers. These mols. may find use as scaffolds for the display of ligands in chemical-biol. applications and as spacers and construction materials for nanoscience applications.

AN 2003:242711 CAPLUS
DN 138:385036
TI The Synthesis of Functionalized Nanoscale Molecular Rods of Defined Length
AU Levins, Christopher G.; Schafmeister, Christian E.
CS Department of Chemistry, University of Pittsburgh, Pittsburgh, PA, 15260, USA
SO Journal of the American Chemical Society (2003), 125(16), 4702-4703
CODEN: JACSAT; ISSN: 0002-7863
PB American Chemical Society
DT Journal
LA English
OS CASREACT 138:385036
IT **526223-02-9P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of functionalized nanoscale mol. rods of defined length)
RN 526223-02-9 CAPLUS
CN 1,2,4-Pyrrolidinetricarboxylic acid, 4-[[(9H-fluoren-9-ylmethoxy)carbonyl]amino]-, 4-methyl 1-(phenylmethyl) ester, (2S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 51 CAPLUS COPYRIGHT 2004 ACS on STN

AB Although the contractile effects of glutamate and related excitatory amino acids on gut smooth muscle strips have been demonstrated, the mechanisms, and particularly the physiol. importance of that action, remain unknown. In this study, glutamate, aspartate, AMPA, quisqualate, cis-ACPD and (2R,4R)-APDC evoked concentration-dependent contraction of isolated adult rat gastric fundus, with EC50 values of 210 μM, 150 μM, 20 μM, 33 μM, 2.7 μM and 7.9 μM, resp. L-SOP (0.1 μM-1.9 mM) did not change the basal tone of the prepns. The maximal contractions evoked by glutamate (20 mM) were 38.83% compared with those elicited by acetylcholine (20 μM). The glutamate-evoked contractions were not affected by atropine, verapamil and nicardipine, blocked by CNQX (0.01 μM), or potentiated by Mg2+ (0.01-100 μM), ketamine (0.01-100 μM) and DL-AP5 (0.1-100 μM), as well as L-trans-2,4-PDC (1-100 μM). Anal. of glutamate's action on rat rectum (EC50 = 44 μM) could only be carried out at the early stages, as half of the prepns. were not affected by glutamate. Only 5 out of 26 human longitudinal and circular smooth muscle prepns. taken from the stomach and three segments of the large intestine were very slightly contracted by glutamate, excluding further anal. The contractile effects of glutamate on rat gut smooth muscles were mediated by multiple GluR (non-NMDA > NMDA > group I/II mGluRs) located primarily on smooth muscle cells but functional GluRs on neurons and/or nerve fibers of myenteric nervous plexuses could not be excluded. To fully understand the physiol. significance of glutamate-evoked contractions in the gut, more research is required, most likely using many different methodol. approaches.

AN 2003:171673 CAPLUS

DN 138:379605

TI A pharmacological analysis of the contractile effects of glutamate on rat and human isolated gut smooth muscle strips

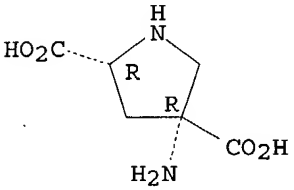
AU Milovanovic, D. R.; Jankovic, S. M.

CS Department of Pharmacology, Medical Faculty, University of Kragujevac, Kragujevac, Yugoslavia

SO Methods and Findings in Experimental and Clinical Pharmacology (2002), 24(10), 661-668

CODEN: MFEPDX; ISSN: 0379-0355
PB Prous Science
DT Journal
LA English
IT **169209-63-6**, (2R,4R)-APDC
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(pharmacol. anal. of contractile effects of glutamate on rat and human isolated gut smooth muscle strips)
RN 169209-63-6 CAPLUS
CN 2,4-Pyrrolidinedicarboxylic acid, 4-amino-, (2R,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



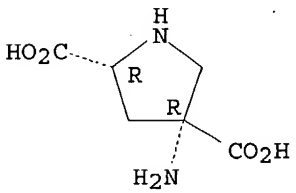
RE.CNT 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 8 OF 51 CAPLUS
AB Two inhibitory responses mediated by both pre- and post-synaptic metabotropic glutamate receptors (mGluRs) were investigated in dopamine neurons of the substantia nigra using whole-cell patch recordings. (2R,4R)-APDC, a group II mGluR agonist, and L-2-amino-4-phosphonobutyrate (L-AP4), a group III mGluR agonist, reversibly suppressed the amplitude of excitatory postsynaptic currents (EPSCs). However, (S)-3,5-DHPG, a group I mGluR agonist, exhibited less inhibitory action on the EPSCs. LY341495, a highly potent group II mGluR antagonist, antagonized the broad spectrum mGluR agonist, 1S,3R-ACPD-induced suppression of EPSCs. In acutely dissociated dopamine neurons, glutamate (Glu) in the presence of CNQX and AP-5 evoked an outward current accompanied by an increase in K+ conductance. (S)-3,5-DHPG, but not (2R,4R)-APDC or L-AP4, also induced an outward current. Glu-induced outward current (IGlu-out) was partially inhibited by LY367385, a selective mGluR1 antagonist, but not by MPEP, a selective mGluR5 antagonist. Ryanodine and cyclopiazonic acid blocked the IGlu-out. In the presence of caffeine, Glu failed to induce a current. Charybdotoxin, but not apamin or iberiotoxin, inhibited the IGlu-out. Taken together, both group II and III mGluRs are mainly involved in the presynaptic inhibition of Glu release to dopamine neurons, while group I mGluRs, including at least mGluR1, participate in the hyperpolarization of dopamine neurons mediated by the opening of charybdotoxin-sensitive Ca2+-activated K+ channels.
AN 2002:982139 CAPLUS
DN 138:363023
TI Characterization of pre- and post-synaptic metabotropic glutamate receptor-mediated inhibitory responses in substantia nigra dopamine neurons
AU Katayama, Jiro; Akaike, Norio; Nabekura, Junichi
CS Graduate School of Medical Science, Cellular and System Physiology, Kyushu University, 3-1-1 Maidashi Higashi-ku, Fukuoka, 812-8582, Japan
SO Neuroscience Research (Oxford, United Kingdom) (2003), 45(1), 101-115
CODEN: NERADN; ISSN: 0168-0102

10/29/04

PB Elsevier Science Ltd.
DT Journal
LA English
IT **169209-63-6**, (2R,4R)-APDC
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(characterization of pre- and post-synaptic metabotropic glutamate receptor-mediated inhibitory neurotransmission responses in substantia nigra dopamine neurons)
RN 169209-63-6 CAPLUS
CN 2,4-Pyrrolidinedicarboxylic acid, 4-amino-, (2R,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

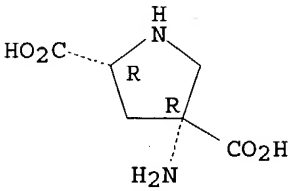


RE.CNT 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 9 OF 51 CAPLUS COPYRIGHT 2004 ACS on STN
AB The enteric nervous system (ENS) contains functional ionotropic and group I metabotropic glutamate (mGlu) receptors. In this study, we determined whether enteric neurons express group II mGlu receptors and the effects of mGlu receptor activation on voltage-gated Ca2+ currents in these cells. (2R,4R)-4-aminopyrrolidine-2,4-dicarboxylate (2R,4R-APDC), a group II mGlu receptor agonist, reversibly suppressed the Ba2+ current in myenteric neurons isolated from the guinea pig ileum. Significant inhibition was also produced by L-glutamate and the group II mGlu receptor agonists, (2S,2'R,3'R)-2-(2',3'-dicarboxycyclopropyl)glycine (DCG-IV) and (2S,1'S,2'S)-2-(2-carboxycyclopropyl)glycine (L-CCG-I), with a rank order potency of 2R,4R-APDC > DCG-IV > L-glutamate > L-CCG-I, and was reduced by the group II mGlu receptor antagonist LY-341495. Pretreatment of neurons with pertussis toxin (PTX) reduced the action of mGlu receptor agonists, suggesting participation of Gi/Go proteins. Finally, ω-conotoxin GVIA blocked current suppression by DCG-IV, suggesting modulation of N-type calcium channels. MGlu2/3 receptor immunoreactivity was displayed by neurons in culture and in the submucosal and myenteric plexus of the ileum. A subset of these cells displayed a glutamatergic phenotype as shown by the expression of vesicular glutamate transporter 2. These results provide the first evidence for functional group II mGlu receptors in the ENS and show that these receptors are PTX sensitive and neg. coupled to N-type calcium channels. Inhibition of N-type calcium channels produced by activation of group II mGlu receptors may modulate enteric neurotransmission.
AN 2002:975106 CAPLUS
DN 138:248822
TI Activation of group II mGlu receptors inhibits voltage-gated Ca2+ currents in myenteric neurons
AU Chen, Wei-Ping; Kirchgessner, Annette L.
CS Department of Physiology and Pharmacology, State University of New York Downstate Medical Center, Brooklyn, NY, 11203, USA
SO American Journal of Physiology (2002), 283(6, Pt. 1), G1282-G1289

CODEN: AJPHAP; ISSN: 0002-9513
PB American Physiological Society
DT Journal
LA English
IT **169209-63-6**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(group II mGlu receptor agonist; activation of group II mGlu receptors inhibits voltage-gated Ca2+ currents in myenteric neurons isolated from ileum)
RN 169209-63-6 CAPLUS
CN 2,4-Pyrrolidinedicarboxylic acid, 4-amino-, (2R,4R)- (9CI) (CA INDEX NAME)

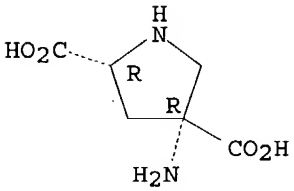
Absolute stereochemistry. Rotation (+).



RE.CNT 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 10 OF 51 CAPLUS COPYRIGHT 2004 ACS on STN
AB The contribution to fear and fear learning of amygdala Group II metabotropic glutamate receptors was examined in rats. Pretest infra-amygdala infusions of the Group II receptor agonist LY354740 (0.3 or 1.0 μg/side) significantly disrupted fear-potentiated startle. The same rats were unimpaired when later tested without drug. The Group II receptor agonist (2R,4R)-4-aminopyrrolidine-2,4-dicarboxylate (3.0 μg/side) mimicked the effect of LY354740, and coadministration of the Group II receptor antagonist LY341495 (0.3 μg/side) prevented it. Pretraining LY354740 (0.3 μg/side) infusions also blocked learning. The effects on learning and performance were significantly less pronounced in rats with misplaced cannulas. Thus, Group II metabotropic receptors within or very near the amygdala regulate fear and fear learning and are a potential target for anxiolytic compds.
AN 2002:973357 CAPLUS
DN 138:232050
TI Group II metabotropic glutamate receptors within the amygdala regulate fear as assessed with potentiated startle in rats
AU Walker, David L.; Rattiner, Lisa M.; Davis, Michael
CS Emory University School of Medicine, USA
SO Behavioral Neuroscience (2002), 116(6), 1075-1083
CODEN: BENEDJ; ISSN: 0735-7044
PB American Psychological Association
DT Journal
LA English
IT **169209-63-6**, (2R,4R)-4-Aminopyrrolidine-2,4-dicarboxylate
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(metabotropic glutamate receptors of Group II within amygdala regulate fear and fear learing as assessed with potentiated startle in rats)
RN 169209-63-6 CAPLUS
CN 2,4-Pyrrolidinedicarboxylic acid, 4-amino-, (2R,4R)- (9CI) (CA INDEX NAME)

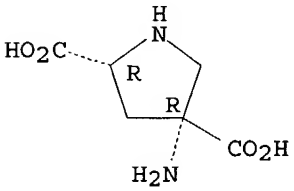
Absolute stereochemistry. Rotation (+).



RE.CNT 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 11 OF 51 CAPLUS COPYRIGHT 2004 ACS on STN
AB Docking of a number of agonists and antagonists into glutamate-binding sites of human metabotropic and ionotropic glutamate receptors was modeled using the computer program AutoDock 3.0. The three-dimensional structures of the ligand-receptor complexes were in good agreement with exptl. data. Effect of water mols. at the ligand-binding site of the receptor on the ligand orientation was studied.
AN 2002:851222 CAPLUS
DN 138:198858
TI Molecular docking of ligands of glutamate receptors
AU Belenikin, M. S.; Makkiarulo, A.; Konstantino, G.; Palyulin, V. A.; Pellichari, P.; Zefirov, N. S.
CS Kafedra Org. Khim., Mosk. Gos. Univ., Moscow, Russia
SO Vestnik Moskovskogo Universiteta, Seriya 2: Khimiya (2002), 43(4), 221-230
CODEN: VMUKA5; ISSN: 0579-9384
PB Izdatel'stvo Moskovskogo Universiteta
DT Journal
LA Russian
IT **169209-63-6**
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(modeling of mol. docking of ligands of human metabotropic and ionotropic glutamate receptors)
RN 169209-63-6 CAPLUS
CN 2,4-Pyrrolidinedicarboxylic acid, 4-amino-, (2R,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

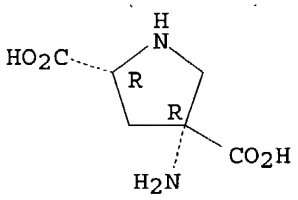


L4 ANSWER 12 OF 51 CAPLUS COPYRIGHT 2004 ACS on STN
AB Although several agonists and antagonists for different subtypes of metabotropic glutamate receptors (mGLURs) have become available in recent years, detailed information regarding their selectivity is not complete in the in vivo animal models. The purpose of the present investigation was

to study the cardiovascular effects of microinjections of some of these mGLUR agonists and antagonists into the nucleus tractus solitarius (nTS). Microinjections (100 nl) of EC50 concns. of 3,5-DHPG (0.005 mM; mGLUR1 agonist), APDC (17.3 mM; mGLUR2/3 agonist), PPG (11.7 mM; mGLUR8 agonist) and L-AP4 (1 mM; mGLUR4 agonist) into the nucleus tractus solitarius of urethane-anesthetized male Wistar rats elicited depressor and bradycardic responses which may be mediated by pre- and/or postsynaptic mechanisms. The blocking effect of mGLUR antagonists used here was not specific for any one type of glutamate receptors (GLURs). For example, AIDA (50 mM; mGLUR1 antagonist) blocked the effects of EC50 concns. of 3,5-DHPG, and PPG. LY341495 (135 mM; mGLUR2/3 antagonist) blocked all of the mGLURs and ionotropic GLURs. EGLU, APICA and MCCG (250 mM each; mGLUR2/3 antagonists) blocked the effects of APDC, NMDA and AMPA. CPPG (80 mM) and MSOP (125 mM), mGLUR4 antagonists, blocked the effects of 3,5-DHPG, PPG and L-AP4. D-AP7 (NMDA receptor antagonist) and NBQX (a non-NMDA receptor antagonist) did not alter the responses of any of the mGLUR agonists. The data presented may be useful in assessing the role of metabotropic and ionotropic GLURs in mediating different cardiovascular reflexes.

AN 2002:762261 CAPLUS
DN 138:50186
TI Cardiovascular responses to activation of metabotropic glutamate receptors in the nTS of the rat
AU Viard, Eddy; Sapru, Hreday N.
CS Department of Neurological Surgery, New Jersey Medical School, Newark, NJ, 07103-2757, USA
SO Brain Research (2002), 952(2), 308-321
CODEN: BRREAP; ISSN: 0006-8993
PB Elsevier Science B.V.
DT Journal
LA English
IT **169209-63-6**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(cardiovascular responses to activation of metabotropic glutamate receptors in nucleus tractus solitarius by excitatory amino acid receptor agonists and antagonists)
RN 169209-63-6 CAPLUS
CN 2,4-Pyrrolidinedicarboxylic acid, 4-amino-, (2R,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



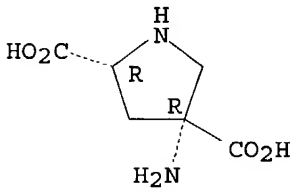
RE.CNT 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 13 OF 51 CAPLUS COPYRIGHT 2004 ACS on STN
AB The aim of this study was to examine whether intrathecal (i.t.) injection of metabotropic glutamate (mGlu) receptor agonists at the thoracolumbar level of the spinal cord causes changes either in the blood pressure or in the heart rate of pentobarbital anesthetized rats. The broad spectrum mGlu receptor agonist (±)-1-aminocyclopentane-trans-1,3-dicarboxylic

acid (trans-ACPD) and the Group III mGluR agonist L-(+)-2-amino-4-phosphonobutyric acid (L-AP4) induced pressor effects at doses of 300 nmol and 600 nmol (i.t.) but did not induce changes at a lower dose (150 nmol, i.t.). The specific Group I mGlu receptor agonist (RS)-3,5-dihydroxyphenylglycine (3,5-DHPG), as well as the highly selective Group II mGlu receptor agonist 2R,4R-4-aminopyrrolidine-2,4-dicarboxylate (2R,4R-APDC), induced pressor effects at a dose of 300 nmol only. The compds. (150-600 nmol) did not modify the heart rate in these expts. Low doses of Group II mGlu receptor agonists (75 nmol 2R,4R-APDC; 1.5 nmol (2S,2'R,3'R)-2-(2',3'-dicarboxychloropropyl)glycine; DCG IV) induced hypotension and bradycardia when spinal N-methyl-D-aspartate (NMDA) receptors were previously blocked by 2-amino-5-phosphonovaleric acid (APV; 30 nmol; i.t.). The pressor response to trans-ACPD was probably mediated by activation of both Group I and Group II mGluRs because i.t. injection of either the selective Group I mGlu receptor antagonist (S)-4-carboxyphenylglycine (4CPG) or the selective Group II mGlu receptor antagonist (2S,3S,4S)-2-methyl-2-(carboxycyclopropyl)glycine (MCCG) antagonized the increases in the blood pressure produced by the agonist. Moreover, 4CPG and MCCG antagonized the pressor effects of 3,5-DHPG and 2R,4R-APDC, resp. Blockade of spinal Group II mGlu receptors by MCCG also prevented the hypotensive and bradycardic effects of 2R,4R-APDC and DCG IV in rats pretreated with APV. The pressor response to L-AP4 (300 nmol) was prevented by the selective antagonist (S)-2-amino-2-methyl-4-phosphonobutanoic acid (MAP4). These results suggest that activation of spinal Group I, II and III mGlu receptors increases the mean blood pressure in pentobarbital anesthetized rats and that, after blockade of NMDA receptors, low doses of Group II mGlu receptor agonists induce hypotension and bradycardia.

AN 2002:713346 CAPLUS
DN 138:83700
TI Activation of spinal metabotropic glutamate receptors elicits cardiovascular responses in pentobarbital anesthetized rats
AU Celuch, Stella Maris; Garcia, Maria del Carmen
CS Instituto de Investigaciones Farmacologicas (CONICET), Buenos Aires, 1113, Argent.
SO Naunyn-Schmiedeberg's Archives of Pharmacology (2002), 366(4), 343-349
CODEN: NSAPCC; ISSN: 0028-1298
PB Springer-Verlag
DT Journal
LA English
IT **169209-63-6**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(metabotropic glutamate receptor agonist; agonist activation of spinal metabotropic glutamate receptors induction of cardiovascular responses in pentobarbital anesthetized rats)
RN 169209-63-6 CAPLUS
CN 2,4-Pyrrolidinedicarboxylic acid, 4-amino-, (2R,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



10/29/04

RE.CNT 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 14 OF 51 CAPLUS COPYRIGHT 2004 ACS on STN

AB Signal transduction mechanisms of group II metabotropic glutamate receptors (mGlu2/3) remains a matter of some controversy, therefore the authors sought to gain new insights into its regulation by studying cAMP production in cultured neurons and astrocytes, and by examining inter-relationships of mGlu2/3-induced signaling with cellular calcium and various signaling cascades. The mGlu2/3 agonists 2R,4R-4-aminopyrrolidine-2,4-dicarboxylic acid (2R,4R-APDC) and (-)-2-oxa-4-aminobicyclo[3.1.0]hexane-4,6-dicarboxylic acid (LY379268) inhibited 10 μM forskolin-stimulated production of cAMP in murine cortical neurons, striatal neurons and forebrain astrocytes in the absence of extracellular Ca2+. These agonists potentiated cAMP production in the presence of 1.8 mM Ca2+ in astrocytes only. This potentiation was dependent on the extracellular Ca2+ concentration (001-10 mM) and inhibited by the mGlu2/3 antagonist LY341495 (1 μM), adenosine deaminase (1 U/mL) and the adenosine A2A receptor antagonist ZM241385 (1 μM). Pre-incubation with the phospholipase C (PLC) inhibitor U73122 (10 μM), L-type Ca2+-channel blockers nifedipine (1 μM) and nimodipine (1 μM), the calmodulin kinase II (CaMKII) inhibitor KN-62 (10 μM) or pertussis toxin (100 ng/mL) inhibited this potentiation. In the absence of 1.8 mM Ca2+, thapsigargin (1 μM) facilitated the potentiation of cAMP production Measurement of the Ca2+-binding dye Fluo-3/AM showed that, compared to Ca2+-free conditions, thapsigargin and 1.8 mM Ca2+ elevated [Ca2+]i in astrocytes; the latter effect being prevented by L-type Ca2+-channel blockers. Potentiation of cAMP production was also demonstrated when astrocytes were stimulated with the β-adrenoceptor agonist isoprenaline (10 μM) in the presence of 1.8 mM Ca2+, but not with the adenosine agonist NECA (10 μM) or the group I mGlu receptor agonist DHPG (100 μM). BaCl2 (1.8 mM) in place of Ca2+ did not facilitate forskolin-stimulated mGlu2/3-potentiation of cAMP. In short, this study in astrocytes demonstrates that under physiol. Ca2+ and adenylate cyclase stimulation an elevation of cAMP production is achieved that is mediated by PLC/IP3- and CaMKII-dependent pathways and results in the release of endogenous adenosine which acts at Gs protein-coupled A2A receptors. These findings provide new insights into mGlu2/3 signaling in brain astrocytes and neurons.

AN 2002:665978 CAPLUS

DN 138:19811

TI Astrocyte mGlu2/3-mediated cAMP potentiation is calcium sensitive: studies in murine neuronal and astrocyte cultures

AU Moldrich, Randal X.; Aprico, Karina; Diwakarla, Shanti; O'Shea, Ross D.; Beart, Philip M.

CS Department of Pharmacology, Monash University, Melbourne, 3800, Australia

SO Neuropharmacology (2002), 43(2), 189-203
CODEN: NEPHBW; ISSN: 0028-3908

PB Elsevier Science Ltd.

DT Journal

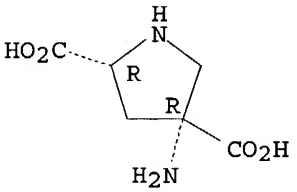
LA English

IT **169209-63-6**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(mGlu2/3 agonist; cAMP and calcium involvement in mGlu2/3 signaling in brain astrocytes and neurons)

RN 169209-63-6 CAPLUS

CN 2,4-Pyrrolidinedicarboxylic acid, 4-amino-, (2R,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RE.CNT 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 15 OF 51 CAPLUS COPYRIGHT 2004 ACS on STN

AB The authors have previously described a neuroprotective action of (2S,2'R,3'R)-2-(2'3'-dicarboxycyclopropyl)glycine (DCG-IV), an agonist for group-II metabotropic receptors, on dopaminergic nerve terminals against the degeneration induced by 1-methyl-4-phenylpyridinium (MPP+). This effect was accompanied by an up-regulation of brain-derived neurotrophic factor (BDNF) mRNA expression in the rat striatum. The authors have now analyzed the phenotypic nature of the BDNF mRNA-expressing cells in response to intrastriatal injection of DCG-IV. Dual in situ hybridization and immunohistochem. revealed that microglial cells but not astrocytes were responsible for this induction. Subsequent anal. demonstrated that this effect was accompanied by striking loss of striatal glutamic acid decarboxylase (GAD) mRNA and massive appearance of internucleosomal DNA fragmentation, a hallmark of apoptosis. A dose-response study demonstrated that doses of DCG-IV as low as 5 nmol was very toxic in terms GAD mRNA and apoptosis. 0.5 nmol of DCG-IV did not induce toxicity at all in terms of GAD mRNA and apoptosis. Activation of group-II metabotropic receptors in striatum with N-Acetyl-Asp-Glu (NAAG; a mGlu3 agonist) and (2R,4R)-4-aminopyrrolidine-2,4-dicarboxylate (a mGlu2 and mGlu3 agonist) did not induce neither loss of GAD mRNA nor appearance of apoptosis (doses ≤20 nmol). In addnl. expts., NAAG, in contrast to DCG-IV, failed to protect the striatal dopaminergic system against the degeneration induced by MPP+ as studied by microdialysis. Finally, the authors studied the mechanism by which DCG-IV is highly toxic. For that, selective antagonists of either metabotropic - (R,S)-α-methyl-4-carboxyphenylglycine and LY 341495 - or ionotropic (N-methyl-D-aspartate, NMDA) - DL-2-amino-5-phosphonovaleric acid (AP-5) glutamate receptors - were co-administered with DCG-IV. Only AP-5 highly protected the striatum against the degeneration induced by DCG-IV. Since DCG-IV also activates the NMDA receptor at concns. higher than 3 μM, it is conceivable that a intrastriatal concentration equal or higher than 3 μM is achieved after a single striatal injection of 5-20 nmol of DCG-IV. The authors findings suggest that much caution must be exerted when testing the numerous neuroprotective effects ascribed to group-II metabotropic receptor activation, in particular when using DCG-IV. The authors conclude that the neuroprotectant capability of a given compound on a specific system does not exclude the possibility of inducing toxicity on a different one.

AN 2002:633472 CAPLUS

DN 138:265486

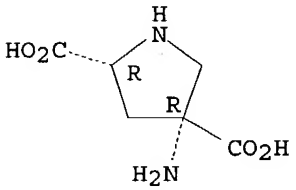
TI DCG-IV but not other group-II metabotropic receptor agonists induces microglial BDNF mRNA expression in the rat striatum. Correlation with neuronal injury

AU Venero, J. L.; Santiago, M.; Tomas-Camardiel, M.; Matarredona, E. R.; Cano, J.; Machado, A.

CS Facultad de Farmacia, Departamento de Bioquimica, Bromatolgoia y

Toxicologia, Universidad de Sevilla, Seville, 41012, Spain
SO Neuroscience (Oxford, United Kingdom) (2002), 113(4), 857-869
CODEN: NRSCDN; ISSN: 0306-4522
PB Elsevier Science Ltd.
DT Journal
LA English
IT **169209-63-6**, (2R,4R)-4-Aminopyrrolidine-2,4-dicarboxylate
RL: ADV (Adverse effect, including toxicity); DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(DCG-IV but not other group-II metabotropic receptor agonists induces microglial BDNF mRNA expression in rat striatum and correlation with neurotoxicity and neuroprotectant capability)
RN 169209-63-6 CAPLUS
CN 2,4-Pyrrolidinedicarboxylic acid, 4-amino-, (2R,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

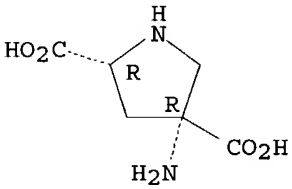


RE.CNT 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 16 OF 51 CAPLUS COPYRIGHT 2004 ACS on STN
AB In the present study, we examined the effects of intrathecal pretreatment (twice daily injections) on postoperative (PO) days 0-3 with the selective Group I (mGluR1a) mGluR antagonist, (RS)-1-aminoindan-1,5-dicarboxylic acid ((RS)-AIDA), the selective Group I (mGluR5a) antagonist, 2-methyl-6-(phenylethynyl)-pyridine (MPEP), the selective Group II mGluR agonist, (2R,4R)-4-aminopyrrolidine-2,4-dicarboxylate ((2R,4R)-APDC) or the selective Group III mGluR agonist, l-2-amino-4-phosphonobutyrate (l-AP4), on mech. and cold hypersensitivity associated with chronic constriction injury (CCI) of the sciatic nerve in rats. Mech. and cold sensitivity was assessed prior to surgery (baseline) and then at 4, 8 and 12 days following CCI. Pretreatment with all of the mGluR agents produced redns. in the development of mech. hypersensitivity. In addition, all the mGluR agents, except MPEP, were effective in reducing the development of cold hypersensitivity. This study demonstrates that spinal Group I mGluR antagonism, and Group II or III mGluR agonism, can effectively decrease the development of mech. and cold hypersensitivity associated with CCI in rats. In addition, the results can be interpreted to suggest that activation of spinal Group I mGluRs contributes to spinal plasticity leading to the development of neuropathic pain, and that this effect is offset by activation of groups II and III mGluRs.
AN 2002:512139 CAPLUS
DN 137:346658
TI Antinociceptive effects following intrathecal pretreatment with selective metabotropic glutamate receptor compounds in a rat model of neuropathic pain
AU Fisher, Kim; Lefebvre, Celeste; Coderre, Terence J.
CS Pain Mechanisms Laboratory, Clinical Research Institute of Montreal,

Montreal, Can.
SO Pharmacology, Biochemistry and Behavior (2002), 73(2), 411-418
CODEN: PBBHAU; ISSN: 0091-3057
PB Elsevier Science Inc.
DT Journal
LA English
IT **169209-63-6**, (2R,4R)-4-Aminopyrrolidine-2,4-dicarboxylate
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antinociceptive effects following intrathecal pretreatment with selective metabotropic glutamate receptor compds. in rat model of neuropathic pain)
RN 169209-63-6 CAPLUS
CN 2,4-Pyrrolidinedicarboxylic acid, 4-amino-, (2R,4R)- (9CI) (CA INDEX NAME)

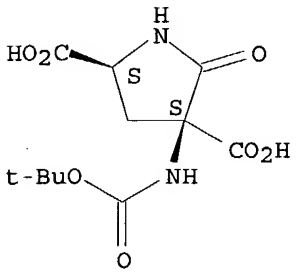
Absolute stereochemistry. Rotation (+).



RE.CNT 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 17 OF 51 CAPLUS COPYRIGHT 2004 ACS on STN
AB A new pathway leading to a mixture of four isomers of 4-aminopyroglutamic acid is described. Michael type addition of Z-ΔAla-OMe to enolates prepared from acylaminomalonates, followed by hydrolysis and decarboxylation give protected 4-aminopyroglutamic acid with the cis:trans ratio approx. 3:2. This mixture was incorporated into Leu-enkephalin (position 2-3). After separation of peptides it appeared that all analogs were essentially inactive in guinea pig ileum and mouse vas deferens bioassays.
AN 2002:156862 CAPLUS
DN 137:353281
TI A novel cis-peptide bond motif inducing β-turn type VI. The synthesis of enkephalin analogues modified with 4-aminopyroglutamic acid
AU Kaczmarek, Krzysztof; Kaleta, Maciej; Chung, Nga N.; Schiller, Peter W.; Zabrocki, Janusz
CS Institute of Organic Chemistry, Technical University of Lodz, Lodz, 90-924, Pol.
SO Acta Biochimica Polonica (2001), 48(4), 1159-1163
CODEN: ABPLAF; ISSN: 0001-527X
PB Polish Biochemical Society
DT Journal
LA English
IT **474797-83-6P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation, isolation and enkephalin related activity of aminopyroglutamates)
RN 474797-83-6 CAPLUS
CN 2,4-Pyrrolidinedicarboxylic acid, 4-[[(1,1-dimethylethoxy)carbonyl]amino]-5-oxo-, (2R,4R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 18 OF 51 CAPLUS COPYRIGHT 2004 ACS on STN

AB The modulation of spontaneous miniature GABAergic inhibitory postsynaptic currents (mIPSC) by the metabotropic glutamate receptors was investigated in the mech. dissociated rat nucleus basalis of Meynert neurons using the conventional whole-cell patch recording configuration. An application of (±)-1-aminocyclopentane-trans-1,3-dicarboxylic acid (tACPD) reversibly reduced the frequency of mIPSC without affecting the current amplitude distribution. The application of K+ channel blockers such as 4-aminopyridine, Cs+, Ba2+ or tetraethylammonium increased the mIPSC frequency, but failed to inhibit the tACPD action on mIPSC. Although the removal of Ca2+ from the extracellular solution reduced the mIPSC frequency, the inhibitory effect of tACPD on mIPSC was unaltered. These results suggested that neither voltage-dependent K+ or Ca2+ channels are involved in the inhibitory effect of tACPD on mIPSC frequency. Forskolin, an activator of adenylate cyclase, facilitated the mIPSC frequency in a concentration-dependent manner and inhibited the tACPD-induced suppression of mIPSC frequency. 8-Br-cAMP, a membrane permeable analog of cAMP, also prevented the inhibitory action of tACPD. However, Sp-cAMP, an activator of protein kinase A, could not prevent the inhibitory action of tACPD. L-CCG-I and (2R,4R)-APDC, group II mGluR agonists, mimicked the tACPD action on mIPSC frequency, but L-AP4, a group III mGluR agonist, had no such effect. MCCG, a group II mGluR antagonist, fully blocked the tACPD action. It was concluded that the activation of group II mGluR on the GABAergic presynaptic nerve terminals projecting to the rat nucleus basalis of Meynert neurons therefore inhibits the GABA release by reducing the activity of the cAMP-dependent pathway.

AN 2002:40665 CAPLUS

DN 136:319651

TI Presynaptic inhibition of GABAergic miniature currents by metabotropic glutamate receptor in the rat CNS

AU Doi, A.; Ishibashi, H.; Jinno, S.; Kosaka, T.; Akaike, N.

CS Cellular and System Physiology, Graduate School of Medicial Sciences, Kyushu University, Fukuoka, 812-8582, Japan

SO Neuroscience (Oxford, United Kingdom) (2002), 109(2), 299-311
CODEN: NRSCDN; ISSN: 0306-4522

PB Elsevier Science Ltd.

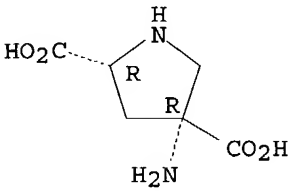
DT Journal

LA English

IT **169209-63-6**, (2R,4R)-APDC
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(metabotropic glutamate receptor presynaptic inhibition of GABAergic

miniature currents in rat Central Nervous System and mechanisms therein)
RN 169209-63-6 CAPLUS
CN 2,4-Pyrrolidinedicarboxylic acid, 4-amino-, (2R,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



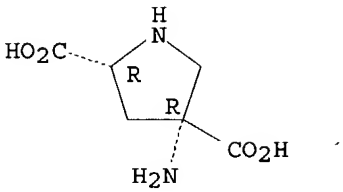
RE.CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 19 OF 51 CAPLUS COPYRIGHT 2004 ACS on STN
AB Agonists of metabolism regulating glutamic acid receptor group-2 are found as inducers of brain-derived neurotrophic factor (BDNF) in the rat. These agonists such as (2S,2'R,3'R)-2-(2',3'-dicarboxycyclopropyl)glycine and (2R,4R)-4-aminopyrrolidine-2,4-dicarboxylate were administered to the brain of the rat, and the increase of BDNF in the brain was demonstrated. Apparently, these agonists activate the biosynthesis of BDNF and are useful for controlling Alzheimer's disease and Parkinsonism.
AN 2002:23489 CAPLUS
DN 136:90953
TI Inducer of brain-derived neurotrophic factor
IN Senba, Ritsuko
PA Foundation for Scientific Technology Promotion, Japan
SO Jpn. Kokai Tokkyo Koho, 4 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI JP 2002003401	A2	20020109	JP 2000-192170	20000627
PRAI JP 2000-192170		20000627		

IT **169209-63-6**, (2R,4R)-4-Aminopyrrolidine-2,4-dicarboxylate
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(as inducer of brain-derived neurotrophic factor for controlling Alzheimer's and Parkinson's diseases)
RN 169209-63-6 CAPLUS
CN 2,4-Pyrrolidinedicarboxylic acid, 4-amino-, (2R,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L4 ANSWER 20 OF 51 CAPLUS COPYRIGHT 2004 ACS on STN

AB The regulation of extracellular glutamate in the nucleus accumbens by group II metabotropic glutamate receptors (mGluR2/3) was examined in vivo. Stimulation of mGluR2/3 with 2R,4R-4-aminopyrrolidine-2,4-dicarboxylate (APDC) or N-acetylaspartyl-glutamate reduced extracellular glutamate levels. Conversely, blockade of mGluR2/3 by LY143495 or (RS)-1-amino-5-phosphonoindan-1-carboxylic acid (APICA) increased extracellular glutamate, an effect antagonized by the coadministration of APDC. These effects likely involve both vesicular and nonvesicular glutamate, because the increase in glutamate by APICA or the decrease by APDC was prevented by blocking N-type calcium channels and the release of glutamate after potassium-induced membrane depolarization was antagonized by APDC. In addition, blockade of the cystine-glutamate exchange, a major nonvesicular source of extracellular glutamate, by (S)-4-carboxyphenylglycine blocked the effects induced by either APDC or APICA. However, blockade of Na+ channels by tetrodotoxin or Na+-dependent glutamate transporters by DL-threo-β-benzyloxyaspartate failed to affect the alterations in extracellular glutamate by APICA or APDC, resp. Group II mGluRs are Gi-coupled and coperfusion with the cAMP-dependent protein kinase (PKA) activator Sp-cAMPS blocked the reduction in glutamate by APDC and the PKA inhibitor Rp-cAMPS prevented the elevation in glutamate by APICA. Taken together, these data support three conclusions: (1) group II mGluRs regulate both vesicular and nonvesicular release of glutamate in the nucleus accumbens, (2) there is tonic in vivo stimulation of mGluR2/3 by endogenous glutamate, and (3) modulation of group II mGluRs of extracellular glutamate is Ca2+- and PKA-dependent.

AN 2002:12148 CAPLUS

DN 136:178260

TI Group II metabotropic glutamate receptors modulate extracellular glutamate in the nucleus accumbens

AU Xi, Zheng-Xiong; Baker, David A.; Shen, Hui; Carson, Daniel S.; Kalivas, Peter W.

CS Department of Physiology and Neuroscience, Medical University of South Carolina, Charleston, SC, USA

SO Journal of Pharmacology and Experimental Therapeutics (2002), 300(1), 162-171
CODEN: JPETAB; ISSN: 0022-3565

PB American Society for Pharmacology and Experimental Therapeutics

DT Journal

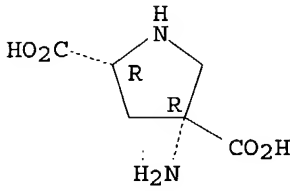
LA English

IT **169209-63-6**
RL: BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(glutamate receptor agonist; group II metabotropic glutamate receptors modulation of vesicular and nonvesicular glutamate release in nucleus accumbens and involved mechanisms)

RN 169209-63-6 CAPLUS

CN 2,4-Pyrrolidinedicarboxylic acid, 4-amino-, (2R,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RE.CNT 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 21 OF 51 CAPLUS COPYRIGHT 2004 ACS on STN

AB The pharmacophore for group I metabotropic glutamate receptor (mGluR1) agonists is revealed and their activity predicted by means of the previously developed and further improved electron-conformational (EC) method. A distinguishing feature of this method is that in addition to revealing the pharmacophore of activity as a set of specific atomic electronic features arranged in a special geometry, it allows for prediction of the activity quant. as a function of the parameters of pharmacophore flexibility and anti-pharmacophore shielding groups. Conformational anal., electronic structure calcns., and matrix processing are performed for the training set of 29 compds., 13 active and 16 inactive, and the pharmacophore of mGluR1 agonists is evaluated. It contains a four-point skeleton of three oxygen atoms and one nitrogen atom at certain interat. distances with restricted atomic interaction indexes whereby all these parameters are determined within certain tolerances. The pharmacophore parameter flexibilities, as well as the influence of the anti-pharmacophore shielding and other auxiliary groups are parameterized and weighted by seven consts., their values being obtained from a least-square regression with very good statistics: R2 = 0.97, F = 589 (.apprx.100% level of confidence), and a standard error of about 5% of the range of measured values. The results are also tested with the leave-one-out cross validation method that yields prediction statistics R2 = 0.91. The E statistics were also evaluated illustrating the role of each of the activity parameters involved.

AN 2001:925011 CAPLUS
DN 136:318765

TI Pharmacophore identification and bioactivity prediction for group I metabotropic glutamate receptor agonists by the electron-conformational QSAR method

AU Rosines, Eran; Bersuker, Isaac B.; Boggs, James E.
CS Institute for Theoretical Chemistry, Department of Chemistry and Biochemistry, The University of Texas at Austin, Austin, TX, 78712, USA

SO Quantitative Structure-Activity Relationships (2001), 20(4), 327-334
CODEN: QSARDI; ISSN: 0931-8771
PB Wiley-VCH Verlag GmbH
DT Journal
LA English

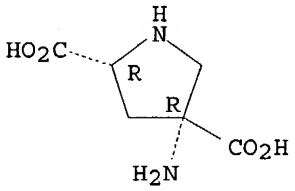
IT **169209-63-6**
RL: PAC (Pharmacological activity); PRP (Properties); BIOL (Biological study)
(pharmacophore identification and bioactivity prediction for group I metabotropic glutamate receptor agonists by electron-conformational QSAR method)

RN 169209-63-6 CAPLUS

10/29/04

CN 2,4-Pyrrolidinedicarboxylic acid, 4-amino-, (2R,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RE.CNT 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 22 OF 51 CAPLUS COPYRIGHT 2004 ACS on STN

AB There is strong evidence for the existence of functional interactions between metabotropic glutamate receptors and dopamine transmission in the nucleus accumbens. In the present study, we investigated the interactions between group II mGlu receptors and D1-like- and D2-like receptors in the rat nucleus accumbens. Administration of the selective group II metabotropic glutamate receptor agonist APDC, which had no effect when injected alone, potentiated the locomotor response produced by the selective D1-like receptor agonist SKF 38393 but had no effect on those induced by the selective D2-like receptor agonist quinpirole (also known as LY 171555) - a compound believed to act only at D2-like presynaptic receptors when injected alone - or co-administration of SKF 38393+quinpirole - a pharmacol. condition thought to stimulate both D1-like receptors and presynaptic and postsynaptic D2-like receptors. In contrast, the selective group II mGlu receptor antagonist LY 341495, which induced an increase in basal locomotor activity, showed no effect on the SKF 38393-induced locomotor response, but abolished that produced by quinpirole or SKF 38393+quinpirole. The present findings demonstrate that stimulation of group II mGlu receptors has a cooperative and potentiating action on the locomotor response induced by D1-like receptor activation, whereas blockade of group II mGlu receptors has an antagonist action on the locomotor responses induced by activation of D2-like receptors. Although these data are consistent from a pharmacol. point of view, as the effects of the group II mGlu receptor antagonist LY 341495 were blocked by the group II mGlu receptor agonist APDC and conversely, the subtle neurochem. crosstalks underlying such a differential effect of group II mGlu receptors on D1-like- and D2-like DA receptors remain to be elucidated.

AN 2001:651763 CAPLUS

DN 136:944

TI Differential modulation of the D1-like- and D2-like dopamine receptor-induced locomotor responses by group II metabotropic glutamate receptors in the rat nucleus accumbens

AU David, H. N.; Abraini, J. H.

CS Centre Cyceron, Universite de Caen, UMR CNRS 6551, Caen, 14074, Fr.

SO Neuropharmacology (2001), 41(4), 454-463
CODEN: NEPHBW; ISSN: 0028-3908

PB Elsevier Science Ltd.

DT Journal

LA English

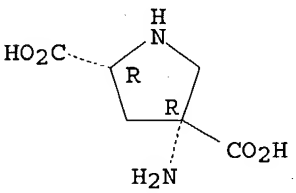
IT **169209-63-6**, (2R,4R)-4-Aminopyrrolidine-2,4-dicarboxylate
RL: BSU (Biological study, unclassified); BIOL (Biological study)

(differential modulation of D1-like- and D2-like dopamine receptor-induced locomotor responses by group II metabotropic glutamate receptors in rat nucleus accumbens)

RN 169209-63-6 CAPLUS

CN 2,4-Pyrrolidinedicarboxylic acid, 4-amino-, (2R,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RE.CNT 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 23 OF 51 CAPLUS COPYRIGHT 2004 ACS on STN

AB [3H]LY 341495 is a highly potent and selective antagonist for group II metabotropic glutamate (mGlu) receptors (mGlu2 and mGlu3), which has been used to label these receptors in cells expressing recombinant receptor subtypes. In this study, we characterized the kinetics, pharmacol., and distribution of [3H]LY 341495 binding to mGlu receptors in rat brain tissue. Equilibrium expts. in the rat forebrain demonstrated binding to a single site that was saturable, reversible, and of high affinity (Bmax, 3.9 pmol/mg of protein, Kd, 0.84 nM). The relative order of potencies for displacement of [3H]LY 341495 by mGlu receptor ligands was LY 341495 >> L-glutamic acid > LY 354740 > (2S,1'S,2'S)-2-(carboxycyclopropyl)glycine > 4-(2R,4R)-aminopyrrolidine-2,4-dicarboxylate > (1S,3R)-1-aminocyclopentane-1,3-dicarboxylic acid > (R,S)-α-methyl-4-phosphonophenylglycine > (R,S)3,5-dihydroxyphenylglycine > L-(+)-2-amino-4-phosphonobutyric acid. [3H]LY 341495 was not displaced by the selective ionotropic glutamate receptor agonists N-methyl-D-aspartic acid, (R,S)-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, or kainate at concns. up to 1 mM. Comparison of [3H]LY 341495 binding in rat brain with recombinant mGlu receptor subtypes demonstrated a very high correlation with mGlu3 receptor binding (r2 = 0.957), a significant, but lower, correlation with mGlu2 receptor binding (r2 = 0.869), but no significant correlation to mGlu8 receptor binding (r2 = 0.284). Regional studies using autoradiog. showed a similar distribution of [3H]LY 341495 binding to that for group II mGlu receptors previously reported by others using immunocytochem. techniques. These studies indicate that [3H]LY 341495 selectively labels group II (mGlu2/3) receptors, but under the conditions used, [3H]LY 341495 may bind predominately to mGlu3 receptor populations in the rat forebrain.

AN 2001:546912 CAPLUS

DN 135:236900

TI [3H]LY341495 binding to group II metabotropic glutamate receptors in rat brain

AU Wright, Rebecca A.; Arnold, M. Brian; Wheeler, William J.; Ornstein, Paul L.; Schoepp, Darryle D.

CS Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN, USA

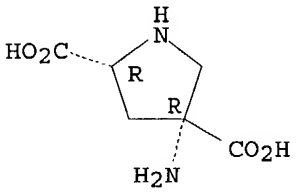
SO Journal of Pharmacology and Experimental Therapeutics (2001), 298(2), 453-460
CODEN: JPETAB; ISSN: 0022-3565

PB American Society for Pharmacology and Experimental Therapeutics

10/29/04

DT Journal
LA English
IT **169209-63-6**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(LY 341495 binding to group II metabotropic glutamate receptors in rat brain and kinetics and pharmacol. and distribution thereof)
RN 169209-63-6 CAPLUS
CN 2,4-Pyrrolidinedicarboxylic acid, 4-amino-, (2R,4R)- (9CI) (CA INDEX NAME)

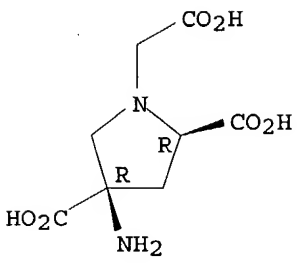
Absolute stereochemistry. Rotation (+).



RE.CNT 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 24 OF 51 CAPLUS COPYRIGHT 2004 ACS on STN
AB The chemical synthesis of a series of N1-substituted derivs. of (2R,4R)-4-aminopyrrolidine-2,4-dicarboxylic acid [(2R,4R)-APDC] as constrained analogs of γ-substituted glutamic acids is described. Appropriate substitution of the N1-position results in agonist, partial agonist, or antagonist activity at mGluR2, mGluR3, and/or mGluR6.
AN 2001:518626 CAPLUS
DN 135:338726
TI Synthesis of N1-substituted analogues of (2R,4R)-4-amino-pyrrolidine-2,4-dicarboxylic acid as agonists, partial agonists, and antagonists of group II metabotropic glutamate receptors
AU Mukhopadhyaya, J. K.; Kozikowski, A. P.; Grajkowska, E.; Pshenichkin, S.; Wroblewski, J. T.
CS Department of Neurology, Drug Discovery Program, Georgetown University Medical Center, Washington, DC, 20007, USA
SO Bioorganic & Medicinal Chemistry Letters (2001), 11(14), 1919-1924
CODEN: BMCLE8; ISSN: 0960-894X
PB Elsevier Science Ltd.
DT Journal
LA English
OS CASREACT 135:338726
IT **371979-01-0P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(synthesis of N1-substituted analogs of (2R,4R)-4-amino-pyrrolidine-2,4-dicarboxylic acid as agonists, partial agonists, and antagonists of group II metabotropic glutamate receptors)
RN 371979-01-0 CAPLUS
CN 2,4-Pyrrolidinedicarboxylic acid, 4-amino-1-(carboxymethyl)-, dihydrochloride, (2R,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



●2 HCl

RE.CNT 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 25 OF 51 CAPLUS COPYRIGHT 2004 ACS on STN

AB Previous studies demonstrated that selected agonists for metabotropic glutamate group II and group III receptors can provide protection against seizures in adult animals. The present study has examined the potential effect of some of these compds. on seizures induced in immature rats by intracerebroventricular infusion of DL-homocysteic acid (DL-HCA, 600 nmol/side). Rat pups were sacrificed during generalized clonic-tonic seizures, 50-60 min after infusion. Comparable time intervals were used for sacrificing the pups which had received the protective drugs. The anticonvulsant effect was evaluated according to the suppression of behavioral manifestations of seizures and the protection of energy metabolite changes which normally accompany these seizures (large decreases of glucose and glycogen, and .apprx.7- to 10-fold accumulation of lactate). Partial protection was exhibited by group II mGluR agonist (2S,2'R,3'R)-2-(2',3'-dicarboxycyclopropyl)glycine (DCG IV, 0.6 nmol) and this effect was abolished after pretreatment with an antagonist for group II mGluRs (RS)-α-methyl-4-tetrazolylphenylglycine (MTPG, 100 nmol). In high doses (5-100 nmol), however, DCG IV evoked seizures which were prevented by AP7, suggesting that the convulsant effect was mediated by interaction with NMDA receptors. A pronounced anticonvulsant effect against DL-HCA-induced seizures was achieved with low doses of a highly selective group II mGluR agonist (2R,4R)-4-aminopyrrolidine-2,4-dicarboxylate (2R,4R-APDC, 0.6 nmol), group II agonist and group I mGluR antagonist (S)-4-carboxy-3-hydroxyphenylglycine ((S)-4-C3HPG, 0.6 nmol) and group III mGluR agonist (RS)-1-amino-3-(phosphonomethylene) cyclobutane-carboxylic acid (32 nmol). Generalized clonic-tonic seizures were completely suppressed and the metabolic changes were markedly ameliorated, there being only a 1.5-, 2- and 2.5-fold rise of lactate, resp. Higher doses of (S)-4-C3HPG (1-100 nmol) were, however, less anticonvulsant than low doses. The present results have confirmed that mGluRs may be considered a potential target for treatment of epilepsy.

AN 2001:502985 CAPLUS
DN 136:452

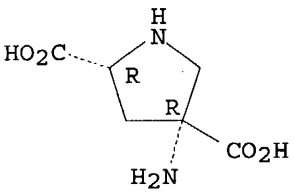
TI Attenuation of seizures induced by homocysteic acid in immature rats by metabotropic glutamate group II and group III receptor agonists

AU Folbergrova, J.; Haugvicova, R.; Mares, P.
CS Institute of Physiology, Academy of Sciences of the Czech Republic, Prague, 142 20, Czech Rep.

SO Brain Research (2001), 908(2), 120-129
CODEN: BRREAP; ISSN: 0006-8993

PB Elsevier Science B.V.
DT Journal
LA English
IT **169209-63-6**, (2R,4R)-4-Aminopyrrolidine-2,4-dicarboxylate
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(attenuation of seizures induced by homocysteic acid in immature rats by metabotropic glutamate group II and group III receptor agonists)
RN 169209-63-6 CAPLUS
CN 2,4-Pyrrolidinedicarboxylic acid, 4-amino-, (2R,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



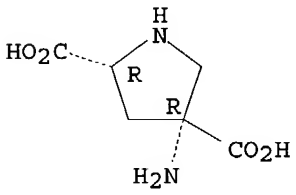
RE.CNT 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 26 OF 51 CAPLUS COPYRIGHT 2004 ACS on STN
AB Since group II metabotropic glutamate (mGlu) receptors are a potential target for the amelioration of neuronal injury, we evaluated the ability of group II mGlu receptor agonists to attenuate toxicity induced by various insults in cortical, striatal and cerebellar granular (CGCs) pure neuronal cultures. The three cultures, when maintained under serum-free, anti-oxidant rich conditions for up to 13 days in vitro (div) were shown by immunocytochem. to contain a maximum of 2-7% glia. At 6, 9 and 13 div a graded pattern of injury to cortical and striatal cultures was achieved with either hydrogen peroxide (60-110 μM), staurosporine (1 μM), N-methyl-D-aspartate (NMDA, 70 μM), α-amino-3-hydroxy-methylisoxazole-4-propionate (AMPA, 100 μM) or kainate (100 μM) over either 4, 24 or 48 h. CGCs were similarly exposed to low K+ (5.4 mM KCl). Cell viability was examined via phase-contrast microscopy and assessed by a 3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyltetrazolium bromide assay. Treatment with group II mGlu receptor agonists (1-300 μM), 2R,4R-4-aminopyrrolidine-2,4-dicarboxylate ((2R,4R)-APDC), (2S,1'S,2'S)-2-(carboxycyclopropyl)glycine (L-CCG-I), (2S,2'R,3'R)-2-(2',3'-dicarboxycyclopropyl)glycine (DCG-IV) and N-acetylaspartylglutamate (NAAG) failed to attenuate the toxicity. Pretreatment of cultures with the agonists and treatment following acute insult also failed to attenuate toxicity. Further investigations demonstrated the presence of second messenger activation whereby (2R,4R)-APDC reduced forskolin-stimulated production of cAMP in each culture. Thus, despite receptor coupling to intracellular signaling cascades, and regardless of culture development, agonist concentration, extent and mode of injury, group II mGlu receptor agonists were unable to protect against injury induced in cortical, striatal and cerebellar granular pure neuronal cultures. This result is in contrast to mixed cultures of neurons and glia and implies an important role for glia in the neuroprotective effects of group II mGlu receptor agonists.
AN 2001:502707 CAPLUS
DN 135:313508

10/29/04

TI Group II mGlu receptor agonists fail to protect against various neurotoxic insults induced in murine cortical, striatal and cerebellar granular pure neuronal cultures
AU Moldrich, R. X.; Giardina, S. F.; Beart, P. M.
CS Department of Pharmacology, Monash University, Clayton, 3800, Australia
SO Neuropharmacology (2001), 41(1), 19-31
CODEN: NEPHBW; ISSN: 0028-3908
PB Elsevier Science Ltd.
DT Journal
LA English
IT **169209-63-6**, 2R,4R-APDC
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(effect of group II mGlu receptor agonists on toxicity induced by various insults in cortical, striatal and cerebellar granular pure neuronal cultures)
RN 169209-63-6 CAPLUS
CN 2,4-Pyrrolidinedicarboxylic acid, 4-amino-, (2R,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

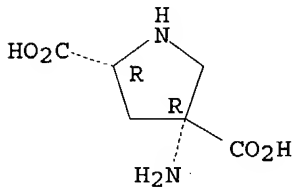


RE.CNT 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 27 OF 51 CAPLUS COPYRIGHT 2004 ACS on STN
AB The anticonvulsant activity of the selective group II metabotropic glutamate receptor (mGlu) agonist 2R,4R-4-aminopyrrolidine-2,4-dicarboxylate (2R,4R-APDC) has been evaluated in chemoconvulsant and sound-induced models of epileptic seizures in DBA/2 mice. 2R,4R-APDC (≥10 nmol, intracerebroventricularly (i.c.v.), -15 min) transiently reduced sound-induced seizure activity including clonic seizures to 40% of vehicle at 20 nmol (i.c.v.) and 30% of vehicle at 100 mg/kg (i.p. (i.p.), -15 min). 2R,4R-APDC inhibited clonic seizures induced by the group III mGlu antagonist (R,S)-α-methylserine-O-phosphate (2.5 μmol, i.c.v.) when co-injected at 20-40 nmol and inhibited limbic seizure activity induced by the mGlu1/5 agonist (R,S)-3,5-dihydroxyphenylglycine (1.5 μmol, i.c.v.) when co-injected at 10-40 nmol. A reversal of the anticonvulsant activity of 2R,4R-APDC was observed at (>20 nmol) in each of the chemoconvulsant and sound-induced models of epileptic seizures. 2R,4R-APDC (0.1-1 μmol, i.c.v.) induced stimulus-independent, rapid and dose-dependent clonic seizures. Selective mGlu2/3 agonists represent a novel class of potential anti-epileptic drugs, however due to the proconvulsant activity observed here, 2R,4R-APDC is obviously limited in this regard.
AN 2001:95875 CAPLUS
DN 134:348181
TI The mGlu2/3 agonist 2R,4R-4-aminopyrrolidine-2,4-dicarboxylate, is anti- and proconvulsant in DBA/2 mice
AU Moldrich, R. X.; Talebi, A.; Beart, P. M.; Chapman, A. G.; Meldrum, B. S.

CS Department of Pharmacology, Monash University, Melbourne, 3800, Australia
SO Neuroscience Letters (2001), 299(1-2), 125-129
CODEN: NELED5; ISSN: 0304-3940
PB Elsevier Science Ireland Ltd.
DT Journal
LA English
IT **169209-63-6**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(mGlu2/3 agonist 2R,4R-4-aminopyrrolidine-2,4-dicarboxylate, is anti- and proconvulsant in DBA/2 mice)
RN 169209-63-6 CAPLUS
CN 2,4-Pyrrolidinedicarboxylic acid, 4-amino-, (2R,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

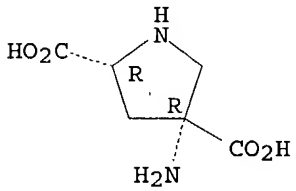


RE.CNT 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 28 OF 51 CAPLUS COPYRIGHT 2004 ACS on STN
AB The stimulation of high-affinity GTPase activity through metabotropic glutamate receptors (mGluRs) was pharmacol. characterized with the use of a series of agonists for mGluRs in rat hippocampal and striatal membranes. The pharmacol. profile of the response was almost identical to each other between both brain regions. Thus, the high-affinity GTPase activities were stimulated by several mGluR-related compds. with the following rank order of potency: (2S,2'R,3'R)-2-(2',3'-dicarboxycyclopropyl)glycine (DCG-IV) = (2S,1'S,2'S)-2-(carboxycyclopropyl)glycine (L-CCG-I) > L-glutamate = 2R,4R-4-aminopyrrolidine-2,4-dicarboxylate [(2R,4R)-APDC] > (S)-4-carboxy-3-hydroxyphenylglycine [(S)-4C3HPG] = 1S,3R-1-aminocyclopentane-1,3-dicarboxylate [(1S,3R)-ACPD] > (S)-3-carboxy-4-hydroxyphenylglycine [(S)-3C4HPG] = ibotenate. The neg. logarithmically transformed EC50 (pEC50) values of these compds. in both brain regions were significantly correlated with those reported previously in the cerebral cortical membranes. On the contrary, other reagents including a selective group I mGluRs agonist, (RS)-3,5-dihydroxyphenylglycine [(RS)-3,5-DHPG], and selective group III mGluRs agonists such as L(+)-2-amino-4-phosphonobutylate (L-AP4) and L-serine-O-phosphate (L-SOP) had little or no effects even at the highest concentration examined Quisqualate was also a very weak agonist in both regions. These results indicate that mGluR-mediated high-affinity GTPase activity derives from the Gi proteins associated with adenylyl cyclase inhibition through group II mGluRs, in particular the mGluR2 subtype, in rat hippocampal and striatal membranes.
AN 2001:9242 CAPLUS
DN 134:66578
TI Stimulation of high-affinity GTPase activity through group II metabotropic glutamate receptors in rat hippocampal and striatal membranes

AU Odagaki, Yuji; Nishi, Nobuyuki; Koyama, Tsukasa
CS Department of Psychiatry, Hokkaido University Graduate School of Medicine, Sapporo, 060-8638, Japan
SO Japanese Journal of Pharmacology (2000), 84(4), 399-404
CODEN: JJPAAZ; ISSN: 0021-5198
PB Japanese Pharmacological Society
DT Journal
LA English
IT **169209-63-6**, (2R,4R)-APDC
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(group II metabotropic glutamate receptor activation stimulation of high-affinity GTPase in rat hippocampal and striatal membranes)
RN 169209-63-6 CAPLUS
CN 2,4-Pyrrolidinedicarboxylic acid, 4-amino-, (2R,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RE.CNT 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 29 OF 51 CAPLUS COPYRIGHT 2004 ACS on STN
AB Activation of heterotrimeric guanine nucleotide-binding regulatory proteins (G-proteins) functionally coupled to metabotropic glutamate receptors (mGluRs) was assessed by agonist-induced high-affinity GTPase (EC3.6.1.-) activity in rat cerebral cortical membranes. L-Glutamate (1 mM) stimulated high-affinity GTPase activity to the same extent throughout the incubation period up to 20 min, in a Mg2+-dependent manner. The addition of 1 mM L-glutamate augmented Vmax of the enzyme activity (1670 to 3850 pmol mg-1 protein 15 min-1) with slight increase in Km value (0.26 to 0.63 μM). The high-affinity GTPase activity was stimulated by the following compds. with a rank order of potency of (2S,2'R,3'R)-2-(2',3'-dicarboxycyclopropyl)g lycine (DCG-IV) > (2S,1'S,2'S)-2-(carboxycyclopyropyl)glycine (L-CCG-I) > L-glutamate ≥ 2R,4R-4-aminopyrrolidine-2,4-dicarboxylate [(2R,4R)-APDC] > 1S,3R-1-aminocyclopentane-1,3-dicarboxylate [(1S,3R)-ACPD] > (S)-4-carboxy-3-hydroxyphenylglycine [(S)-4C3HPG] > (S)-3-carboxy-4-hydroxyphenylglycine [(S)-3C4HPG] > ibotenate, but not by L-(+)-2-amino-4-phosphonobutyrate (L-AP4), (RS)-3,5-dihydroxyphenylglycine [(RS)-3,5-DHPG], quisqualate, or L-serine-O-phosphate (L-SOP), indicative of involvement of group II mGluRs, in particular mGluR2. (2S)-α-Ethylglutamate (EGLU), a presumably selective antagonist against group II mGluRs, inhibited DCG-IV-stimulated high-affinity GTPase activity in a competitive manner with an apparent KB of 220 μM. L-Glutamate-stimulated activity was eliminated by pretreatment of the membranes with sulfhydryl alkylating agent N-ethylmaleimide (NEM) at 30-50 μM, indicating that G-proteins of the Gi family are involved. These results indicate that mGluR agonist-induced high-affinity GTPase activity in rat cerebral cortical membranes may be used to detect the functional

interaction between group II mGluRs, in particular mGluR2, and NEM-sensitive Gi proteins.

AN 2000:578312 CAPLUS

DN 133:233165

TI Pharmacological characterization of metabotropic glutamate receptor-mediated high-affinity GTPase activity in rat cerebral cortical membranes

AU Nishi, Nobuyuki; Odagaki, Yuji; Koyama, Tsukasa

CS Department of Psychiatry, Hokkaido University School of Medicine, Sapporo, 060-8638, Japan

SO British Journal of Pharmacology (2000), 130(7), 1664-1670
CODEN: BJPCBM; ISSN: 0007-1188

PB Nature Publishing Group

DT Journal

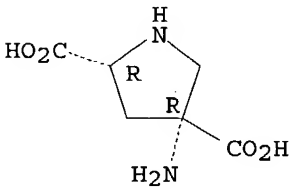
LA English

IT **169209-63-6**, (2R,4R)-APDC
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(pharmacol. characterization of metabotropic glutamate receptor-mediated high-affinity GTPase activity in rat cerebral cortical membranes)

RN 169209-63-6 CAPLUS

CN 2,4-Pyrrolidinedicarboxylic acid, 4-amino-, (2R,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

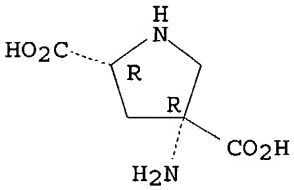
L4 ANSWER 30 OF 51 CAPLUS COPYRIGHT 2004 ACS on STN

AB In the brain, group-III metabotropic glutamate (mGlu) receptors mGlu4, mGlu7 and mGlu8 receptors play a critical role in controlling the release process at many glutamatergic synapses. The pharmacol. profile of mGlu4 receptor has been studied extensively, allowing us to propose a pharmacophore model for this receptor subtype. Surprisingly, the activity of only a few compds. have been reported on mGlu7 and mGlu8 receptors. In order to identify new possibilities for the design of selective compds. able to discriminate between the members of the group-III mGlu receptors, we have undertaken a complete pharmacol. characterization of mGlu8 receptor and compared it with that of mGlu4 receptor, using the same expression system, and the same read out. The activities of 32 different mols. revealed that these two mGlu receptors subtypes share a similar pharmacol. profile. Only small differences were noticed in addition to that previously reported with S-carboxyglutamate (S-Gla) being a partial agonist at mGlu4 receptor and a full antagonist at mGlu8 receptor. These include: a slightly higher relative potency of the agonists 1S,3R and 1S,3S-aminocyclopentane-1,3-dicarboxylic acid (ACPD), S-4-carboxyphenylglycine (S-4CPG) and S-4-carboxy-3-hydroxyphenylglycine (S-4C3HPG), and a slightly higher potency of the antagonists LY 354740 and

RS-α-methyl-4-phosphonophenylglycine (MPPG) on mGlu8 receptor. When superimposed on the mGlu4 receptor pharmacophore model, these mols. revealed three regions that may be different between the ligand binding sites of mGlu8 and mGlu4 receptors.

AN 2000:256024 CAPLUS
DN 133:13023
TI Pharmacological characterization of the rat metabotropic glutamate receptor type 8a revealed strong similarities and slight differences with the type 4a receptor
AU De Colle, C.; Bessis, A.-S.; Bockaert, J.; Acher, F.; Pin, J.-P.
CS Centre INSERM-CNRS de Pharmacologie-Endocrinologie, UPR 9023-CNRS, Montpellier, 34094, Fr.
SO European Journal of Pharmacology (2000), 394(1), 17-26
CODEN: EJPHAZ; ISSN: 0014-2999
PB Elsevier Science B.V.
DT Journal
LA English
IT **169209-63-6**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(rat metabotropic glutamate receptor type 8a pharmacol. characterization and comparison with mGluR4a and pharmacophore models therefor)
RN 169209-63-6 CAPLUS
CN 2,4-Pyrrolidinedicarboxylic acid, 4-amino-, (2R,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



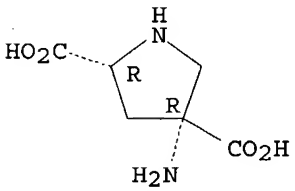
RE.CNT 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 31 OF 51 CAPLUS COPYRIGHT 2004 ACS on STN
AB Mammalian metabotropic glutamate receptors (mGluRs) are classified into 3 groups based on their sequence similarity and ligand recognition selectivity. Recently, we identified a Drosophila mGluR (DmGluAR) which is about equidistant, phylogenetically, from the 3 mGluR groups. However, both the G-protein coupling selectivity and the pharmacol. profile of DmGluAR, as analyzed with mutated G-proteins and a few compds., look similar to those of mammalian group-II mGluRs. In the present study we carefully examined the pharmacol. profile of DmGluAR, and compared it to those of the rat mGlu1a, mGlu2 and mGlu4a receptors, representative of group-I, II and III resp. The pharmacol. profile of DmGluAR was found to be similar to that of mGlu2R, and only very small differences could be identified at the level of their pharmacophore models. These data strongly suggest that the binding sites of these two receptors are similar. To further document this idea, a 3D model of the mGlu2 binding domain was constructed based on the low sequence similarity with periplasmic amino acid binding proteins, and was used to identify the residues that possibly constitute the ligand recognition pocket.

Interestingly, this putative binding pocket was found to be very well conserved between DmGluAR and the mammalian group-II receptors. These data indicate that there has been a strong selective pressure during evolution to maintain the ligand recognition selectivity of mGluRs.

AN 2000:236781 CAPLUS
DN 133:69122
TI Conservation of the ligand recognition site of metabotropic glutamate receptors during evolution
AU Parmentier, M.-L.; Galvez, T.; Acher, F.; Peyre, B.; Pellicciari, R.; Grau, Y.; Bockaert, J.; Pin, J.-P.
CS Centre INSERM-CNRS de Pharmacologie-Endocrinologie, UPR 9023-CNRS, Montpellier, 34094, Fr.
SO Neuropharmacology (2000), 39(7), 1119-1131
CODEN: NEPHBW; ISSN: 0028-3908
PB Elsevier Science Ltd.
DT Journal
LA English
IT **169209-63-6**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(metabotropic glutamate receptors ligand-binding site conservation during evolution)
RN 169209-63-6 CAPLUS
CN 2,4-Pyrrolidinedicarboxylic acid, 4-amino-, (2R,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



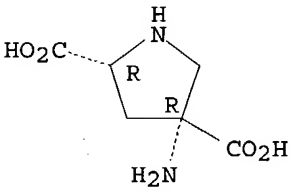
RE.CNT 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 32 OF 51 CAPLUS COPYRIGHT 2004 ACS on STN
AB Group II metabotropic glutamate receptors (mGluR 2/3) are distributed differentially across the layers of cat visual cortex, and this distribution varies with age. At 3-4 wk, mGluR 2/3 receptor immunoreactivity is present in all layers. By 6-8 wk of age, it is still present in extragranular layers (2, 3, 5, and 6) but has disappeared from layer 4, and dark-rearing postpones the disappearance of Group II receptors from layer 4. We examined the physiol. effects of Group II activation, to see if these effects varied similarly. The responses of single neurons in cat primary visual cortex were recorded to visual stimulation, then the effect of iontophoresis of 2R,4R-4 aminopyrrolidine-2,4-dicarboxylate (2R,4R-APDC), a Group II specific agonist, was observed in animals between 3 wk and adulthood. The effect of 2R,4R-APDC was generally suppressive, reducing both the visual response and spontaneous activity of single neurons. The developmental changes were in agreement with the immunohistochem. results: 2R,4R-APDC had effects on cells in all layers in animals of 3-4 wk but not in layer 4 of animals >6 wk old. Moreover, the effect of 2R,4R-APDC was reduced in the cortex of older animals (>22 wk). Dark-rearing animals to 47-54 days

maintained the effects of 2R,4R-APDC in layer 4. The disappearance of Group II mGluRs from layer 4 between 3 and 6 wk of age is correlated with the segregation of ocular dominance columns in that layer, raising the possibility that mGluRs 2/3 are involved in this process.

AN 1999:496986 CAPLUS
DN 131:295787
TI Effect of the group II metabotropic glutamate agonist, 2R,4R-APDC, varies with age, layer, and visual experience in the visual cortex
AU Beaver, C. J.; Ji, Q.-H.; Daw, N. W.
CS Department of Ophthalmology and Visual Science, Yale University School of Medicine, New Haven, CT, 06520-8061, USA
SO Journal of Neurophysiology (1999), 82(1), 86-93
CODEN: JONEA4; ISSN: 0022-3077
PB American Physiological Society
DT Journal
LA English
IT **169209-63-6**, 2R,4R-4-Aminopyrrolidine-2,4-dicarboxylate
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(group II metabotropic glutamate agonist effect on visual cortex neurotransmission varies with age and layer and visual experience in cats)
RN 169209-63-6 CAPLUS
CN 2,4-Pyrrolidinedicarboxylic acid, 4-amino-, (2R,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

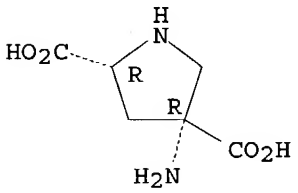


RE.CNT 63 THERE ARE 63 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 33 OF 51 CAPLUS COPYRIGHT 2004 ACS on STN
AB A wide variety of conformationally constrained glutamate analogs, active as group I or group II metabotropic glutamate receptor agonists, were employed in a mol. modeling study aimed at the definition of group I and group II agonist pharmacophoric models. The results of this study can be summarized as follows: (i) Recognition sites of both group I and group II mGluRs can adequately be described by five-point pharmacophores. (ii) An extended conformation of glutamate is required for interaction with both group I and group II mGluRs. Group I receptors, however, can also be activated by a more folded conformation if only four pharmacophore points are considered. (iii) Conformational preferences are, however, not sufficient to explain the potency and selectivity of the whole set of ligands. Volume comparison anal. allowed us to define steric environments for group I and group II mGluRs. Group I mGluRs are characterized by a region of allowed volume in proximity of the distal acidic function, whereas group II mGluRs are characterized by a small polar pocket whose occupancy confers high potency and selectivity. Finally, our study points out the necessity of a careful anal. of the energetic requirements needed to attain the putative bioactive conformations and of explicitly considering

the conformational mobility of carboxylate groups.
AN 1999:465812 CAPLUS
DN 131:222997
TI Pharmacophore Models of Group I and Group II Metabotropic Glutamate Receptor Agonists. Analysis of Conformational, Steric, and Topological Parameters Affecting Potency and Selectivity
AU Costantino, Gabriele; Macchiarulo, Antonio; Pellicciari, Roberto
CS Istituto di Chimica e Tecnologia del Farmaco, Perugia, I-06123, Italy
SO Journal of Medicinal Chemistry (1999), 42(15), 2816-2827
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
IT **169209-63-6**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(pharmacophore models of group I and group II metabotropic glutamate receptor agonists)
RN 169209-63-6 CAPLUS
CN 2,4-Pyrrolidinedicarboxylic acid, 4-amino-, (2R,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

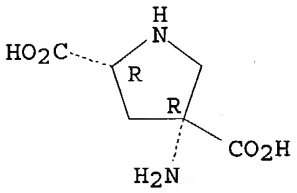


RE.CNT 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 34 OF 51 CAPLUS COPYRIGHT 2004 ACS on STN
AB The synthesis of the 1-amino derivative of (2R,4R)-4-aminopyrrolidine-2,4-dicarboxylic acid (1-amino-APDC), a selective metabotropic glutamate ligand, is disclosed. This compound acts as a partial agonist of the group II mGluRs and shows pronounced neuroprotective properties in the NMDA model of cell toxicity.
AN 1999:404112 CAPLUS
DN 131:170607
TI 1-amino-APDC, a partial agonist of group II metabotropic glutamate receptors with neuroprotective properties
AU Kozikowski, Alan P.; Araldi, Gian Luca; Tuckmantel, Werner; Pshenichkin, Sergey; Surina, Elena; Wroblewski, Jarda T.
CS Georgetown University Medical Center, Drug Discovery Laboratory, Institute for Cognitive and Computational Sciences, Washington, DC, 20007-2197, USA
SO Bioorganic & Medicinal Chemistry Letters (1999), 9(12), 1721-1726
CODEN: BMCLE8; ISSN: 0960-894X
PB Elsevier Science Ltd.
DT Journal
LA English
IT **169209-63-6**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of 1-amino-APDC, a partial agonist of group II metabotropic

glutamate receptors with neuroprotective properties)
RN 169209-63-6 CAPLUS
CN 2,4-Pyrrolidinedicarboxylic acid, 4-amino-, (2R,4R)- (9CI) (CA INDEX NAME)

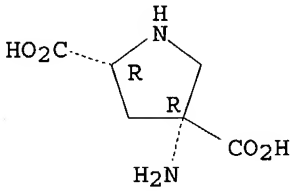
Absolute stereochemistry. Rotation (+).



RE.CNT 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 35 OF 51 CAPLUS COPYRIGHT 2004 ACS on STN
AB To investigate the structural requirements for selective activation or blockade of metabotropic glutamate receptors, a pharmacophore model for group I (mGluR1) and group II (mGluR2) agonists was developed. The Apex-3D program was used with a training set of known active, inactive, and/or selective compds. with a wide structural diversity. The pharmacophore models were then validated by testing a set of addnl. known agonists. Competitive antagonist superpositions were also used in order to define more precisely the topol. of the mGluR1 and mGluR2 agonists' recognition site. Both models account for the activity of most potent compds. and show that the selectivity between mGluR1 and mGluR2 subtypes may be due to excluded vols. and addnl. binding sites, while the relative spatial position of functional groups (NH2, α- and γ-CO2H) remains very similar. On both models glutamate lies in an extended form. An addnl. binding site is disclosed on mGluR1, while this region would be forbidden on mGluR2. This new site combines a closed and an open model for mGluR1 and accounts for the increased affinity of quisqualic acid. The models show another large hydrophobic region which is tolerated for mGluR2 and restricted for mGluR1.
AN 1999:250929 CAPLUS
DN 131:67631
TI Agonist selectivity of mGluR1 and mGluR2 metabotropic receptors: a different environment but similar recognition of an extended glutamate conformation
AU Jullian, Nathalie; Brabet, Isabelle; Pin, Jean-Philippe; Acher, Francine C.
CS Parc Club Orsay Universite, Molecular Simulations Inc., Orsay, 91893, Fr.
SO Journal of Medicinal Chemistry (1999), 42(9), 1546-1555
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
IT **169209-63-6**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(structural requirements for selective activation or blockade of mGluR1 and mGluR2 metabotropic receptors)
RN 169209-63-6 CAPLUS
CN 2,4-Pyrrolidinedicarboxylic acid, 4-amino-, (2R,4R)- (9CI) (CA INDEX NAME)

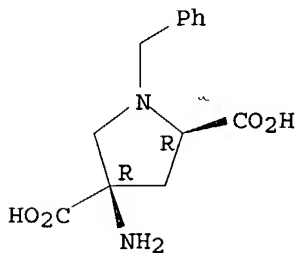
Absolute stereochemistry. Rotation (+).



RE.CNT 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 36 OF 51 CAPLUS COPYRIGHT 2004 ACS on STN
AB A series of N1-substituted derivs. of (2R,4R)-4-aminopyrrolidine-2,4-dicarboxylate (2R,4R-APDC) has been prepared as constrained analogs of γ-substituted glutamic acids and examined for their effects at recombinant metabotropic glutamate receptor (mGluR) subtypes in vitro. Appropriate substitution of the N1 position of 2R,4R-APDC resulted in the identification of a number of selective group II mGluR antagonists.
AN 1998:554710 CAPLUS
DN 129:254357
TI Synthesis and metabotropic glutamate receptor antagonist activity of N1-substituted analogs of 2R,4R-4-aminopyrrolidine-2,4-dicarboxylic acid
AU Valli, Matthew J.; Schoepp, Darryle D.; Wright, Rebecca A.; Johnson, Bryan G.; Kingston, Ann E.; Tomlinson, Rosemarie; Monn, James A.
CS Discovery Chemistry Research, Eli Lilly and Company, Indianapolis, IN, 46285, USA
SO Bioorganic & Medicinal Chemistry Letters (1998), 8(15), 1985-1990
CODEN: BMCLE8; ISSN: 0960-894X
PB Elsevier Science Ltd.
DT Journal
LA English
IT **171336-76-8P**
RL: PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis and metabotropic glutamate receptor antagonist activity of N1-substituted analogs of 2R,4R-4-aminopyrrolidine-2,4-dicarboxylic acid)
RN 171336-76-8 CAPLUS
CN 2,4-Pyrrolidinedicarboxylic acid, 4-amino-1-(phenylmethyl)-, (2R,4R)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RE.CNT 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 37 OF 51 CAPLUS COPYRIGHT 2004 ACS on STN

AB Recordings were made from single neurons responsive to somatosensory input in the ventrobasal thalamus of the anesthetized rat. GABAergic afferent inhibition arising from the thalamic reticular nucleus was evoked using a condition-test vibrissal stimulation paradigm. Local iontophoretic application of the group II metabotropic glutamate receptor (mGluR) agonist 2R,4R-4-aminopyrrolidine-2,4-dicarboxylate (2R,4R-APDC) in the vicinity of the recorded neurons produced a reduction of the afferent inhibition (from 78% to 25%), presumably via a presynaptic mechanism. This effect could be antagonized by LY307452, a known group II mGluR antagonist. In contrast, two selective group I mGluR agonists, (S)-3,5-dihydroxyphenylglycine (DHPG) and trans-azetidine-2,4-dicarboxylate (tADA), were without effect on the GABAergic inhibition. These data show that group II but not group I mGluRs can have a significant role in the modulation of GABAergic afferent inhibition in the ventrobasal thalamus. This could be of importance in the control of sensory discriminative processes and functions of sleep, arousal and seizure generation.

AN 1998:379092 CAPLUS
DN 129:198294

TI Modulation of sensory inhibition in the ventrobasal thalamus via activation of group II metabotropic glutamate receptors by 2R,4R-aminopyrrolidine-2,4-dicarboxylate

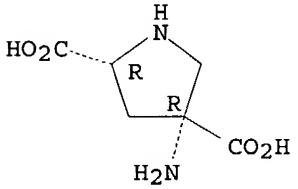
AU Salt, T. E.; Turner, J. P.
CS Institute of Ophthalmology, University College London, 11-43 Bath Street, London, EC1V 9EL, UK

SO Experimental Brain Research (1998), 121(2), 181-185
CODEN: EXBRAP; ISSN: 0014-4819
PB Springer-Verlag
DT Journal
LA English

IT **169209-63-6**, 2R,4R-Aminopyrrolidine-2,4-dicarboxylic acid
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(modulation of sensory inhibition in the ventrobasal thalamus via activation of group II metabotropic glutamate receptors by 2R,4R-aminopyrrolidine-2,4-dicarboxylate)

RN 169209-63-6 CAPLUS
CN 2,4-Pyrrolidinedicarboxylic acid, 4-amino-, (2R,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RE.CNT 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

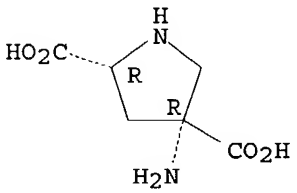
L4 ANSWER 38 OF 51 CAPLUS COPYRIGHT 2004 ACS on STN

AB The presinaptic modulation of glutamatergic neurotransmission in vivo by

agonists of group II mGluRs (e.g. (2R,4R)-4-aminopyrrolidine-2,4-dicarboxylate) is a strategy for reducing glutamate neurotransmission in the striatum. This approach using mGluR agonists might have a potential clin. use in the long-term therapy of Parkinson's disease. However, this remains to be explored further in future studies using systematically applied mGluR agonists.

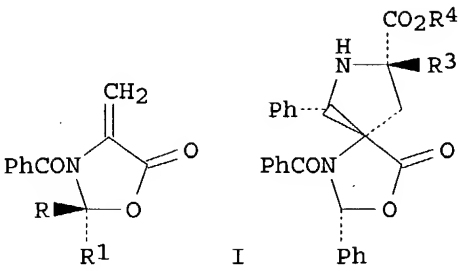
AN 1998:376198 CAPLUS
DN 129:144776
TI Inhibition of glutamate and aspartate release in vivo by (2R,4R)-4-aminopyrrolidine-2,4-dicarboxylate, a selective agonist of group II metabotropic glutamate receptors
AU Battaglia, Giuseppe; Perry, Kenneth W.; Monn, James A.; Schoepp, Darryle D.
CS Central Nervous System Research, Eli Lilly and Co., Lilly Corporate Center, Indianapolis, IN, 46285, USA
SO Portland Press Proceedings (1998), 12(Metabotropic Glutamate Receptors and Brain Function), 235-241
CODEN: POPPEF; ISSN: 0966-4068
PB Portland Press Ltd.
DT Journal
LA English
IT **169209-63-6**, (2R,4R)-4-Aminopyrrolidine-2,4-dicarboxylate
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition of glutamate and aspartate release in vivo by (2R,4R)-4-aminopyrrolidine-2,4-dicarboxylate, a selective agonist of group II metabotropic glutamate receptors)
RN 169209-63-6 CAPLUS
CN 2,4-Pyrrolidinedicarboxylic acid, 4-amino-, (2R,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



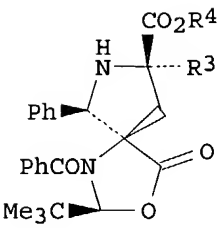
RE.CNT 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 39 OF 51 CAPLUS COPYRIGHT 2004 ACS on STN
GI

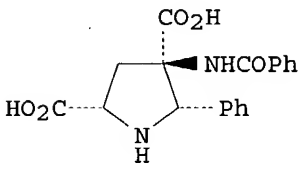


I

II



III



IV

AB The 1,3-dipolar cycloaddn. reactions of the title oxazolidinones I (R = H, R1 = Ph; R = CMe3, R1 = H) with the azomethine ylides PhCH:NCHR3CO2R4 (R3 = Me, CH2CHMe2, Ph, CH2Ph, H; R4 = Me, Et), derived from N-benzylidene α-amino acid esters, proceed with good to high diastereoselectivity giving mainly the exo-cycloadducts II and III. The cycloaddn. adducts can be converted to highly functionalized prolines, e.g., IV, in high enantiomeric purity. The Michael addition adducts of I with the azomethine ylides derived from N-(disubstituted methylidene) α-amino acid esters allow for a practical synthesis of all four stereoisomers of 4-benzamidopyroglutamate. The stereochem. of these cycloaddn. and Michael adducts has been extensively determined by single-crystal x-ray structural anal. Lithium-chelated transition state structures have been proposed to rationalize the stereochem. outcomes of these reactions.

AN 1998:243963 CAPLUS
DN 129:16079

TI Diastereoselective 1,3-dipolar cycloadditions and Michael reactions of azomethine ylides to (2R)-3-benzoyl-4-methylidene-2-phenyloxazolidin-5-one and (2S)-3-benzoyl- 2-t-butyl-4-methylideneoxazolidin-5-one

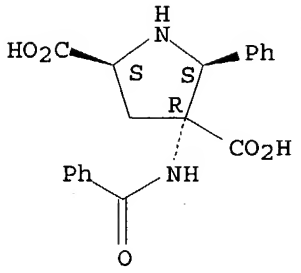
AU Pyne, Stephen G.; Safaei, Javad; Schafer, A. Karl; Javidan, Abdollah; Skelton, Brian W.; White, Allan H.
CS Department of Chemistry, University of Wollongong, Wollongong, 2522, Australia

SO Australian Journal of Chemistry (1998), 51(2), 137-158
CODEN: AJCHAS; ISSN: 0004-9425
PB CSIRO Publishing
DT Journal
LA English

IT **207796-16-5P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(diastereoselective dipolar cycloaddns. and Michael reactions of azomethine ylides to oxazolidinones)

RN 207796-16-5 CAPLUS
CN 2,4-Pyrrolidinedicarboxylic acid, 4-(benzoylamino)-5-phenyl-, (2S,4R,5S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RE.CNT 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 40 OF 51 CAPLUS COPYRIGHT 2004 ACS on STN

AB The effects of intracerebral administration of the group II metabotropic glutamate receptor agonist, 2R,4R-4-aminopyrrolidine-2,4-dicarboxylate (2R,4R-APDC), were tested on both the development of amygdaloid kindling and on fully developed stage 5 amygdala kindled seizures. The development of amygdaloid kindling was significantly retarded in 2R,4R-APDC (10 nmol in 0.5 μl) treated animals compared to control animals over a period of 8 days. At a low dose, 2R,4R-APDC (0.1 nmol) caused a 42.5% increase of the generalized seizure threshold in fully kindled animals. As higher doses were administered, however, the changes in generalized seizure threshold were less marked, and even a small decrease in the threshold was seen (-19.6% at 10 nmol). The agonist 2R,4R-APDC inhibited depolarization-induced release of [3H]d-aspartate from cortical synaptosomes with an IC50 value of 0.29 μM. This effect was maximal at 1 μM, and decreased with dose thereafter. These findings suggest that the selective activation of the group II metabotropic glutamate receptors by agonists such as 2R,4R-APDC may be of therapeutic potential in the treatment of seizure disorders.

AN 1998:195855 CAPLUS
DN 129:431

TI Specific group II metabotropic glutamate receptor activation inhibits the development of kindled epilepsy in rats

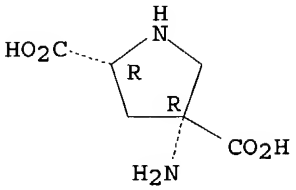
AU Attwell, P. J. E.; Koumentaki, A.; Croucher, M. J.; Bradford, H. F.
CS Department of Biochemistry, Imperial Coll. Sci. Technology and Medicine, London, SW7 2AZ, UK

SO Brain Research (1998), 787(2), 286-291
CODEN: BRREAP; ISSN: 0006-8993
PB Elsevier Science B.V.
DT Journal
LA English

IT **169209-63-6**, 2R,4R-4-Aminopyrrolidine-2,4-dicarboxylate
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(specific group II metabotropic glutamate receptor activation by 2R,4R-APDC inhibits development of kindled epilepsy in rats)

RN 169209-63-6 CAPLUS
CN 2,4-Pyrrolidinedicarboxylic acid, 4-amino-, (2R,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RE.CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

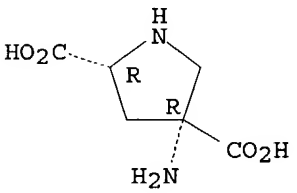
L4 ANSWER 41 OF 51 CAPLUS COPYRIGHT 2004 ACS on STN

AB The interactive effects of different metabotropic glutamate (mGlu) receptor subtypes to regulate phosphoinositide turnover have been studied in neonatal rat cerebral cortex and hippocampus by use of agonists and antagonists selective between group I and II mGlu receptors. The group II-selective agonist 2R,4R-4-aminopyrrolidine-2,4-dicarboxylate (2R,4R-APDC; 100 μM) had no effect on basal total inositol phosphate ([3H]-InsPx) accumulation (in the presence of Li+) in myo-[3H]-inositol pre-labeled slices, but enhanced the maximal [3H]-InsPx response to the group I-selective agonist (S)-3,5-dihydroxyphenylglycine (DHPG) by about 100% in both hippocampus and cerebral cortex. In cerebral cortex the enhancing effect of 2R,4R-APDC occurred with respect to the maximal responsiveness and had no effect on EC50 values for DHPG (-log EC50 (M): control, 5.56; +2R,4R-APDC, 5.51). 2R,4R-APDC also caused a significant enhancement of the DHPG-stimulated inositol 1,4,5-trisphosphate (Ins(1,4,5)P3) mass response over an initial 0-300 s time-course. The enhancing effects of 2R,4R-APDC on DHPG-stimulated [3H]-InsPx accumulation were observed in both the presence and nominal absence of extracellular Ca2+, and irresp. of whether 2R,4R-APDC was added before, simultaneous with, or subsequent to DHPG. Furthermore, increasing the tissue cAMP concentration up to 100-fold had no effect on DHPG-stimulated Ins(1,4,5)P3 accumulation in the absence or presence of 2R,4R-APDC. 2R,4R-APDC and (2S, 1'R, 2'R, 3'R)-2-(2,3-dicarboxylcyclopropyl)glycine (DCG-IV), the latter agent in the presence of MK-801 to prevent activation of NMDA-receptors, each inhibited forskolin-stimulated cAMP accumulation by about 50%, with resp. EC50 values of 1.3 and 0.04 μM (-log EC 50 (M): 2R,4R-APDC, 5.87; DCG-IV, 7.38). In the presence of DHPG (30 μM), 2R,4R-APDC and DCG-IV also concentration-dependently increased [3H]-InsPx accumulation with resp. EC50 values of 4.7 and 0.28 μM (-log EC50 (M): 2R,4R-APDC, 5.33; DCG-IV, 6.55) which were 3-7-fold rightward-shifted relative to the adenylyl cyclase inhibitory responses. The group II-selective mGlu receptor antagonist LY307452 (30 μM) caused parallel rightward shifts in the concentration-effect curves for inhibition of forskolin-stimulated adenylyl cyclase, and enhancement of DHPG-stimulated [3H]-InsPx accumulation, by 2R,4R-APDC yielding similar equilibrium dissociation consts. (Kds, 3.7 and 4.1 μM resp.) for each response. The ability of 2R,4R-APDC to enhance receptor-mediated [3H]-InsPx accumulation appeared to be agonist-specific; thus although DHPG (100 μM) and the muscarinic cholinoceptor agonist carbachol (10 μM) stimulated similar [3H]-InsPx accumulations, only the response to the former agonist was enhanced by co-activation of group II mGlu receptors. These data demonstrate that second messenger-generating phosphoinositide responses stimulated by group I mGlu receptors are pos. modulated by co-activation of group II mGlu receptors in cerebral cortex and hippocampus. The data presented here are discussed with respect to the possible mechanisms which might mediate the modulatory activity, and

the physiol. and pathophysiol. significance of such crosstalk between mGlu receptors.

AN 1998:122153 CAPLUS
DN 128:253227
TI Regulation of phosphoinositide turnover in neonatal rat cerebral cortex by group I- and II- selective metabotropic glutamate receptor agonists
AU Mistry, Rajendra; Golding, Nicki; Challiss, R. A. John
CS Department of Cell Physiology and Pharmacology, University of Leicester, Leicester, LE1 9HN, UK
SO British Journal of Pharmacology (1998), 123(3), 581-589
CODEN: BJPCBM; ISSN: 0007-1188
PB Stockton Press
DT Journal
LA English
IT **169209-63-6**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(phosphoinositide turnover regulation in neonatal rat cerebral cortex and hippocampus by group I- and II- selective metabotropic glutamate receptor agonists)
RN 169209-63-6 CAPLUS
CN 2,4-Pyrrolidinedicarboxylic acid, 4-amino-, (2R,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



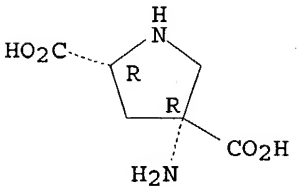
RE.CNT 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 42 OF 51 CAPLUS COPYRIGHT 2004 ACS on STN
AB Metabotropic glutamate receptors have been implicated in modulation of synaptic transmission in many different systems. This study reports the effects of selective activation of metabotropic glutamate receptors on synaptic transmission in intracellularly recorded locus ceruleus neurons in brain slice prepns. Perfusion of either L-2-amino-4-phosphonobutyric acid (L-AP4; 0.1-500 μM) or (±)-1-aminocyclopentane-trans-1,3,dicarboxylic acid (t-ACPD; 0.1-500 μM) caused a depression of excitatory postsynaptic potentials in a dose-dependent fashion to about 70% inhibition. Both agonists exerted their effects at relatively low concns. with estimated EC50s of 2.6 μM and 11.5 μM for L-AP4 and t-ACPD, resp. This inhibition was not observed with the potent group I metabotropic glutamate receptor agonist (RS)-3,5-dihydroxyphenylglycine (DHPG; 100 μM). Conversely, (R)-4-carboxy-3-hydroxyphenyl-glycine (4C-3H-PG), a group I antagonist/group II agonist, and 2R,4R-4-aminopyrrolidine-2,4-dicarboxylate (APDC), a novel and specific group II agonist, also caused an inhibition of excitatory postsynaptic potentials. Both t-ACPD and L-AP4 produced an increase in paired-pulse facilitation, and failed to change the locus ceruleus response to focally applied glutamate, indicating a presynaptic locus of action. The L-AP4 inhibition was

antagonized by (S)-amino-2-methyl-4-phosphonobutanoic acid (MAP4; group III antagonist) but not by (RS)-α-methyl-4-carboxyphenylglycine [(RS)-MCPG; mixed antagonist], suggesting that this agonist acts through a type 4 metabotropic glutamate receptor. Conversely, t-ACPD was antagonized by MCPG and by Et glutamate (group II antagonist), but not by aminoindan dicarboxylic acid (AIDA; group I antagonist) or MAP4, suggesting that this agonist acts on a type 2 or 3 metabotropic glutamate receptor. Taken together, these results suggest that two pharmacol. distinct presynaptic metabotropic glutamate receptors function in an additive fashion to inhibit excitatory synaptic transmission in locus ceruleus neurons. These receptors may be involved in a feedback mechanism and as such may function as autoreceptors for excitatory amino acids.

AN 1997:536845 CAPLUS
DN 127:200427
TI Modulation of excitatory synaptic transmission in locus ceruleus by multiple presynaptic metabotropic glutamate receptors
AU Dube, G. R.; Marshall, K. C.
CS Department of Physiology, Faculty of Medicine, University of Ottawa, Ottawa, ON, K1H 8M5, Can.
SO Neuroscience (Oxford) (1997), 80(2), 511-521
CODEN: NRSCDN; ISSN: 0306-4522
PB Elsevier
DT Journal
LA English
IT **169209-63-6**, 2R,4R-4-Aminopyrrolidine-2,4-dicarboxylate
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(excitatory synaptic transmission in locus ceruleus modulation by multiple presynaptic metabotropic glutamate receptors)
RN 169209-63-6 CAPLUS
CN 2,4-Pyrrolidinedicarboxylic acid, 4-amino-, (2R,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



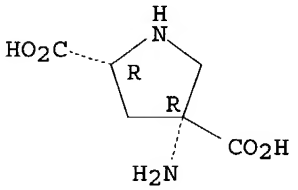
RE.CNT 71 THERE ARE 71 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 43 OF 51 CAPLUS COPYRIGHT 2004 ACS on STN
AB The mGlu receptor subtypes and second messenger pathways that mediate 1S,3R-1-aminocyclopentane-1,3-dicarboxylic acid (1S,3R-ACPD) responses in brain tissues are not fully understood. 1S,3R-ACPD differs from 3,5-dihydroxyphenylglycine (DHPG) or quisqualate in that 1S,3R-ACPD also activates group 2 mGlu receptors (mGlu2 and mGlu3) that are neg. linked to cAMP formation. To investigate the contribution of group 2 mGlu receptor activity of 1S,3R-ACPD to the phosphoinositide response in the rat hippocampus, we examined the effects of the novel group 2 mGlu receptor agonist 2R,4R-4-aminopyrrolidine-2,4-dicarboxylate (2R,4R-APDC). 2R,4R-APDC did not activate or inhibit group 1 mGlu receptors (human mGlu1α and mGlu5a) or group 3 mGlu receptors (human mGlu4 and

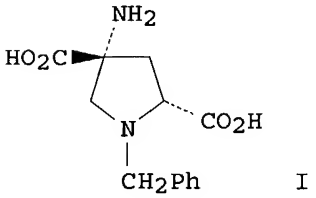
mGlu7), but potently decreased forskolin-stimulated cAMP formation in human mGlu2- and mGlu3-expressing cells. In slices of the adult rat hippocampus 2R,4R-APDC had no effect on basal phosphoinositide hydrolysis; however, it was found to greatly enhance phosphoinositide hydrolysis to DHPG or quisqualate. In the neonatal rat hippocampus, 2R,4R-APDC enhanced the potency of DHPG, while not affecting the maximal response to group 1 mGlu receptor agonists. Thus, the phosphoinositide response in the rat hippocampus to 1S,3R-ACPD is mediated by a synergistic interaction between group 1 and group 2 mGlu receptors.

AN 1997:199525 CAPLUS
DN 126:272659
TI The novel metabotropic glutamate receptor agonist 2R,4R-APDC potentiates stimulation of phosphoinositide hydrolysis in the rat hippocampus by 3,5-dihydroxyphenylglycine: evidence for a synergistic interaction between group 1 and group 2 receptors
AU Schoepp, D. D.; Salhoff, C. R.; Wright, R. A.; Johnson, B. G.; Burnett, J. P.; Mayne, N. G.; Belagaje, R.; Wu, S.; Monn, J. A.
CS Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN, 46285, USA
SO Neuropharmacology (1997), Volume Date 1996, 35(12), 1661-1672
CODEN: NEPHBW; ISSN: 0028-3908
PB Elsevier
DT Journal
LA English
IT **169209-63-6**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(metabotropic glutamate receptor agonist 2R,4R-APDC potentiates stimulation of phosphoinositide hydrolysis in hippocampus by dihydroxyphenylglycine)
RN 169209-63-6 CAPLUS
CN 2,4-Pyrrolidinedicarboxylic acid, 4-amino-, (2R,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L4 ANSWER 44 OF 51 CAPLUS COPYRIGHT 2004 ACS on STN
GI



I

AB The synthesis of the 1-benzyl derivative of (2R,4R)-4-aminopyrrolidine-2,4-dicarboxylic acid (I) starting from cis-4-hydroxy-D-proline is disclosed together with a study of the activity of this compound at metabotropic glutamate receptors (mGluRs). The title compound I (1-benzyl-APDC) was found to display good mGluR6 selectivity, and may thus be a useful pharmacol. research tool.

AN 1997:188941 CAPLUS

DN 126:277738

TI Synthesis, molecular modeling, and biology of the 1-benzyl derivative of APDC - an apparent mGluR6 selective ligand

AU Tuckmantel, Werner; Kozikowski, Alan P.; Wang, Shaomeng; Pshenichkin, Sergey; Wroblewski, Jarda T.

CS Georgetown University Medical Center, Drug Discovery Laboratory, Institute for Cognitive and Computational Sciences, Washington, DC, 20007-2197, USA

SO Bioorganic & Medicinal Chemistry Letters (1997), 7(5), 601-606
CODEN: BMCLE8; ISSN: 0960-894X

PB Elsevier

DT Journal

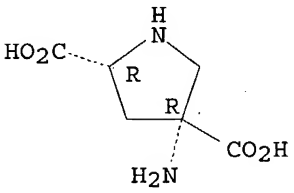
LA English

IT **169209-63-6P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(synthesis, mol. modeling, and metabotropic glutamate receptor antagonist activity of aminopyrrolidinedicarboxylate derivs.)

RN 169209-63-6 CAPLUS

CN 2,4-Pyrrolidinedicarboxylic acid, 4-amino-, (2R,4R)- (9CI) (CA INDEX NAME)

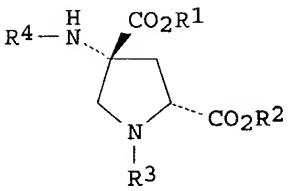
Absolute stereochemistry. Rotation (+).



RE.CNT 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 45 OF 51 CAPLUS COPYRIGHT 2004 ACS on STN

GI



I

AB The present invention provides pyrrolidinyl dicarboxylic acid derivs. I

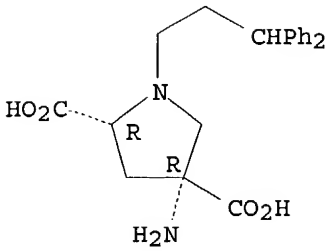
wherein: R1 and R2 are each individually H or a carboxy protecting group; R4 is H or an amino protecting group; R3 = e.g., C1-16 alkyl, C3-8 cycloalkyl; C3-8 cycloalkenyl, aryl, that affect certain excitatory amino acid receptors (no data), and are useful in the treatment of neurol. disorders and psychiatric disorders. This invention further provides novel pyrrolidinyl di-carboxylic acid derivs. and pharmaceutical formulations employing these novel compds. Thus, cis-4-hydroxy-D-proline was esterified and N-benzylated to provide (2R,4R) Et 1-benzyl-4-hydroxypyrrolidine-2-carboxylate; this was oxidized to the 4-oxo derivative which was treated with KCN/ammonium carbonate to afford (2R,4R) di-Et 1-benzyl-4-aminopyrrolidine-2,4-dicarboxylate; the latter was N-protected and debenzylated to afford (2R,4R) di-Et 4-(BOC-amino)pyrrolidine-2,4-dicarboxylate (II) as the scaffold intermediate. Reductive alkylation of II with pentanal afforded (2R,4R) di-Et 4-(BOC-amino)-1-pentylpyrrolidine-2,4-dicarboxylate which was deprotected and hydrolyzed to (2R,4R) 4-amino-1-pentylpyrrolidine-2,4-dicarboxylic acid (I; R1 = R2 = R4 = H, R3 = pentyl).

AN 1996:410401 CAPLUS
DN 125:86486
TI (2R,4R)-4-Aminopyrrolidine-2,4-dicarboxylic acid derivatives as metabotropic glutamate receptor antagonists
IN Monn, James Allen; Tizzano, Joseph Patrick; Valli, Matthew J.
PA Eli Lilly and Co., USA
SO PCT Int. Appl., 97 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9605828	A1	19960229	WO 1995-US10320	19950814
	W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM				
	RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	CA 2198242	AA	19960229	CA 1995-2198242	19950814
	AU 9533252	A1	19960314	AU 1995-33252	19950814
	JP 10504569	T2	19980506	JP 1995-508157	19950814
	EP 703218	A1	19960327	EP 1995-305800	19950821
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
PRAI	US 1994-295337		19940824		
	WO 1995-US10320		19950814		

OS MARPAT 125:86486
IT **178415-98-0P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
((2R,4R)-4-aminopyrrolidine-2,4-dicarboxylic acid derivs. as metabotropic glutamate receptor antagonists)
RN 178415-98-0 CAPLUS
CN 2,4-Pyrrolidinedicarboxylic acid, 4-amino-1-(3,3-diphenylpropyl)-, (2R,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 46 OF 51 CAPLUS COPYRIGHT 2004 ACS on STN

AB The four isomers of 4-aminopyrrolidine-2,4-dicarboxylate (APDC) were prepared and evaluated for their effects at glutamate receptors in vitro. (2R,4R)-APDC (2a), an aza analog of the nonselective mGluR agonist (1S,3R)-1-aminocyclopentane-1,3-dicarboxylate ((1S,3R)-ACPD, 1), was found to possess relatively high affinity for metabotropic glutamate receptors (mGluRs) (ACPD-sensitive [3H]glutamate binding IC50 = 6.49±1.21 μM) with no effects on radioligand binding to NMDA, AMPA, or kainate receptors up to 100 μM. None of the other APDC isomers showed significant mGluR binding affinity, indicating that this interaction is highly stereospecific. Both 1 and 2a were effective in decreasing forskolin-stimulated cAMP formation in the adult rat cerebral cortex (EC50 = 8.17±2.21 μM for 1; EC50 = 14.51±5.54 μM for 2a); however, while 1 was also effective in stimulating basal tritiated inositol monophosphate production in the neonatal rat cerebral cortex (EC50 = 27.7±5.2 μM), 2a (up to 100 μM) was ineffective in stimulating phosphoinositide hydrolysis in this tissue preparation, further supporting our previous observations that 2a is a highly selective agonist for mGluRs neg. coupled to adenylate cyclase. Microelectrophoretic application of either 1 or 2a to intact rat spinal neurons produced an augmentation of AMPA-induced excitation (95±10% increase for 1, 52±6% increase for 2a). Intracerebral injection of 1 (400 nmol) produced characteristic limbic seizures in mice which are not mimicked by 2a (200-1600 nmol, ic). However, the limbic seizures induced by 1 were blocked by systemically administered 2a in a dose-dependent manner (EC50 = 271 mg/kg, i.p.). It is concluded that (2R,4R)-APDC (2a) is a highly selective, systemically-active agonist of mGluRs neg. coupled to adenylate cyclase and that selective activation of these receptors in vivo can result in anticonvulsant effects.

AN 1996:383040 CAPLUS

DN 125:104243

TI Synthesis of the Four Isomers of 4-Aminopyrrolidine-2,4-dicarboxylate: Identification of a Potent, Highly Selective, and Systemically-Active Agonist for Metabotropic Glutamate Receptors Negatively Coupled to Adenylate Cyclase

AU Monn, James A.; Valli, Matthew J.; Johnson, Bryan G.; Salhoff, Craig R.; Wright, Rebecca A.; Howe, Trevor; Bond, Ann; Lodge, David; Spangle, Larry A.; et al.

CS Core Technology Division, Eli Lilly and Company, Indianapolis, IN, USA

SO Journal of Medicinal Chemistry (1996), 39(15), 2990-3000
CODEN: JMCMAR; ISSN: 0022-2623

PB American Chemical Society

DT Journal

LA English

OS CASREACT 125:104243

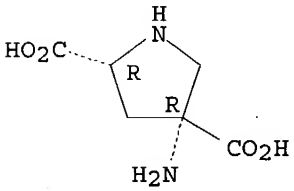
IT **169209-63-6P**, (2R,4R)-4-Aminopyrrolidine-2,4-dicarboxylate
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(synthesis of four isomers of 4-aminopyrrolidine-2,4-dicarboxylate as agonists for metabotropic glutamate receptors neg. coupled to adenylate cyclase)

RN 169209-63-6 CAPLUS

CN 2,4-Pyrrolidinedicarboxylic acid, 4-amino-, (2R,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L4 ANSWER 47 OF 51 CAPLUS COPYRIGHT 2004 ACS on STN

AB A pharmacol. approach was used to investigate the cellular mechanism and metabotropic glutamate receptor (mGluR) subtypes that mediate stimulation of basal cAMP formation in slices of the neonatal rat hippocampus. (1S,3R)-1-Aminocyclopentane-1,3-dicarboxylic acid (1S,3R-ACPD), which is an agonist for phosphoinositide-coupled and inhibitory-coupled cAMP-linked mGluRs in cloned and in situ prepns., produced prominent stimulations of basal cAMP levels (5-10-fold). However, the agonists 3,5-dihydroxyphenylglycine (DHPG) and (2R,4R)-4-aminopyrrolidine-2,4-dicarboxylate (2R,4R-APDC), which selectively act on phosphoinositide-coupled and inhibitory cAMP-coupled mGluRs, resp., only weakly increased cAMP levels. When these 2 mGluR subtype-selective agonists were added in combination, robust increases in cAMP levels, similar to those observed for 1S,3R-ACPD, were found. Stimulations of cAMP content evoked by 1S,3R-ACPD and combined addns. of DHPG plus 2R,4R-APDC occurred at concns. of these agents that directly couple to other mGluR second messenger responses. However, these stimulatory cAMP responses were prevented by the presence of adenosine deaminase and 8-p-sulfophenyltheophylline (an adenosine receptor antagonist), as well as (+)-α-methyl-4-carboxyphenylglycine (an mGLuR receptor antagonist). Thus, 1S,3R-ACPD-induced increases in cAMP formation in the neonatal rat hippocampus are mediated by a synergistic interaction between mGluRs coupled to phosphoinositide (group 1) and inhibitory cAMP (group 2), which are indirectly expressed by potentiation of cAMP responses to other agonists (in this case, endogenous adenosine).

AN 1996:240803 CAPLUS

DN 124:308230

TI (1S,3R)-1-Aminocyclopentane-1,3-dicarboxylic acid-induced increases in cyclic AMP formation in the neonatal rat hippocampus are mediated by a synergistic interaction between phosphoinositide- and inhibitory cyclic AMP-coupled mGluRs

AU Schoepp, Darryle D.; Johnson, Bryan G.; Monn, James A.

CS Central Nervous System Research, Eli Lilly and Company, Indianapolis, IN, USA

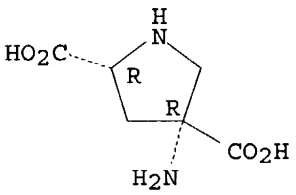
SO Journal of Neurochemistry (1996), 66(5), 1981-5
CODEN: JONRA9; ISSN: 0022-3042

PB Lippincott-Raven

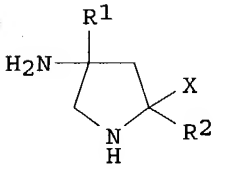
10/29/04

DT Journal
LA English
IT **169209-63-6**, (2R,4R)-4-Aminopyrrolidine-2,4-dicarboxylate
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(aminocyclopentanedicarboxylate-induced increases in cAMP formation in neonatal rat hippocampus are mediated by synergistic interaction between phosphoinositide- and inhibitory cAMP-coupled mGluRs)
RN 169209-63-6 CAPLUS
CN 2,4-Pyrrolidinedicarboxylic acid, 4-amino-, (2R,4R)- (9CI) (CA INDEX NAME)

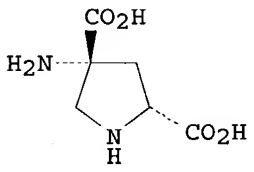
Absolute stereochemistry. Rotation (+).



L4 ANSWER 48 OF 51 CAPLUS COPYRIGHT 2004 ACS on STN
GI



I



II

AB The present invention provides title compds. I where R1 and R2 are independently carboxylic acid or 5-tetrazolyl, or a pharmaceutically acceptable salt or solvate thereof, that affect certain excitatory amino acid receptors, and are useful in the treatment of neurol. disorders and psychiatric disorders (no data). Thus, e.g., hydrolysis of di-Et (2R,4R)-4-(tert-butyloxycarbonylamino)pyrrolidine-2,4-dicarboxylate (preparation given) afforded title derivative (2R,4R)-4-aminopyrrolidine-2,4-dicarboxylic acid (II). Pharmaceutical formulations were given.
AN 1996:34902 CAPLUS
DN 124:203095
TI Pyrrolidinyl dicarboxylic acid derivatives as metabotropic glutamate receptor agonists
IN Monn, James A.; Schoepp, Darryle D.; Valli, Matthew J.
PA Eli Lilly and Co., USA
SO U.S., 12 pp.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5473077	A	19951205	US 1994-337801	19941114

EP 711755	A1	19960515	EP 1995-308031	19951109	
EP 711755	B1	20000531			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE					
AT 193529	E	20000615	AT 1995-308031	19951109	
ES 2146718	T3	20000816	ES 1995-308031	19951109	
CA 2204767	AA	19960523	CA 1995-2204767	19951113	
WO 9615108	A1	19960523	WO 1995-US14675	19951113	
W: AL, AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, TJ, TM, TT, UA, UG, UZ, VN					
RW: KE, LS, MW, SD, SZ, UG, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG					
AU 9642818	A1	19960606	AU 1996-42818	19951113	
JP 10508855	T2	19980902	JP 1995-516228	19951113	
PRAI US 1994-337801	A	19941114			
WO 1995-US14675	W	19951113			

OS MARPAT 124:203095

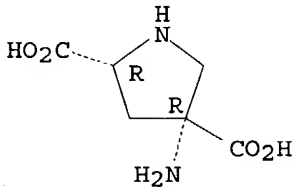
IT **169209-63-6P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(pyrrolidinyl dicarboxylic acid derivs. as metabotropic glutamate receptor agonists)

RN 169209-63-6 CAPLUS

CN 2,4-Pyrrolidinedicarboxylic acid, 4-amino-, (2R,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



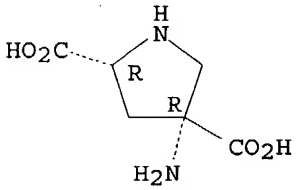
L4 ANSWER 49 OF 51 CAPLUS COPYRIGHT 2004 ACS on STN

AB Metabotropic glutamate receptors (mGluRs) are a heterogeneous family of G-protein coupled receptors that are linked to multiple second messengers in the rat hippocampus. The compound 1S,3R-1-aminocyclopentane-1,3-dicarboxylic acid (1S,3R-ACPD) has been widely used to active this class of receptors and study their functions in situ. However, 1S,3R-ACPD acts on multiple mGluR subtypes to produce multiple alterations in second messengers. The authors report here that the aza-substituted analog of 1S,3R-ACPD, 2R,4R-4-aminopyrrolidine-2,4-dicarboxylate (2R,4R-APDC), is a highly selective agonist for neg.-coupled cAMP-linked mGluRs in the rat hippocampus, with similar potency in mGluR2 expressing cells. 1S,3R-ACPD decreases forskolin-stimulated cAMP formation, increases basal cAMP formation, and increases phosphoinositide hydrolysis in the rat hippocampus. However, 2R,4R-APDC inhibited forskolin-stimulated cAMP, but had none of the other activities of 1S,3R-ACPD. Furthermore, 2R,4R-APDC had no measurable ionotropic glutamate receptor affinity in rat hippocampus, as indicated by lack of effects on basal and glutamate agonist-evoked [3H]norepinephrine release. 2R,4R-APDC also inhibited forskolin-stimulated cAMP formation in human mGluR2 expressing cells with about three-fold greater potency than 1S,3R,ACPD, but unlike 1S,3R-ACPD,

showed no appreciable activation of phosphoinositide hydrolysis in human mGluR1α expressing cells. Thus, 2R,4R-APDC should be a useful pharmacol. agent to explore the functions of mGluRs coupled to inhibition of adenylate cyclase.

AN 1995:796417 CAPLUS
DN 123:246629
TI Selective inhibition of forskolin-stimulated cyclic AMP formation in rat hippocampus by a novel mGluR agonist, 2R,4R-4-aminopyrrolidine-2,4-dicarboxylate
AU Schoepp, D. D.; Johnson, B. G.; Salhoff, C. R.; Valli, M. J.; Desai, M. A.; Burnett, J. P.; Mayne, N. G.; Monn, J. A.
CS Lilly Research Laboratories, Eli Lilly and Co., Indianapolis, IN, 46285, USA
SO Neuropharmacology (1995), 34(8), 843-50
CODEN: NEPHBW; ISSN: 0028-3908
PB Elsevier
DT Journal
LA English
IT **169209-63-6**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(selective inhibition of forskolin-stimulated cAMP formation in rat hippocampus by a novel mGluR agonist, 2R,4R-4-aminopyrrolidine-2,4-dicarboxylate)
RN 169209-63-6 CAPLUS
CN 2,4-Pyrrolidinedicarboxylic acid, 4-amino-, (2R,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



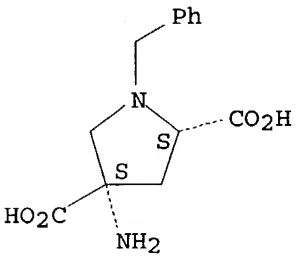
L4 ANSWER 50 OF 51 CAPLUS COPYRIGHT 2004 ACS on STN
AB Asym. syntheses of the title compds. were performed from trans-4-hydroxy-L-proline as homochiral starting material via spirohydantoin ring formation by Bucherer-Bergs reaction of the 4-oxoproline derivs.
AN 1995:784536 CAPLUS
DN 124:9374
TI Asymmetric syntheses of all four isomers of 4-amino-4-carboxyproline: novel conformationally restricted glutamic acid analogs
AU Tanaka, Ken-ichi; Sawanishi, Hiroyuki
CS Faculty of Pharmaceutical Science, Hokuriku University, Kanazawa, 920-11, Japan
SO Tetrahedron: Asymmetry (1995), 6(7), 1641-56
CODEN: TASYE3; ISSN: 0957-4166
PB Elsevier
DT Journal
LA English
OS CASREACT 124:9374
IT **171336-75-7P**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(asym. syntheses of aminocarboxyproline stereoisomers as conformationally restricted Glu analogs)

RN 171336-75-7 CAPLUS

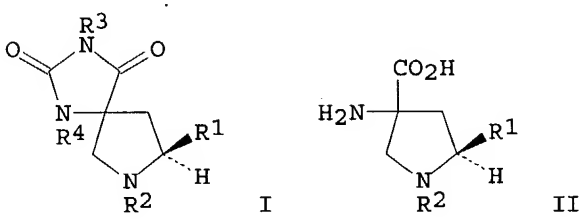
CN 2,4-Pyrrolidinedicarboxylic acid, 4-amino-1-(phenylmethyl)-, (2S-cis)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L4 ANSWER 51 OF 51 CAPLUS COPYRIGHT 2004 ACS on STN

GI



AB The title compds. including spiropyrrolidineimidazoline derivs. (I; R1 = C1-6 alkyl, alkoxyalkyl, alkoxycarbonyl, hydroxyalkyl, CO2H; R2 = H, C1-6 alkyl, aryl, phenylalkyl, carbamoylalkyl, diphenylalkyl; R3, R4 = H, C1-6 alkyl, ester group) and aminopyrrolidinecarboxylic acid derivs. (II; R1, R2 = same as above), useful as anticonvulsants with low toxicity, are prepared Thus, ethylation of Me L-hydroxyprolinate with EtI in CH2Cl2 containing Et3N at 60° gave (2S,4R)-1-ethyl-4-hydroxy-2-methoxycarbonylpyrrolidine. Swern oxidation of the latter compound with (COCl)2 and DMSO in CH2Cl2 containing Et3N at -60° gave (2S)-1-ethyl-4-oxo-2-methoxycarbonylpyrrolidine which underwent Bucherer-Bergs reaction with KCN and ammonium carbonate in 60% aqueous MeOH at 55-60° to give (3R,5S)-1-ethyl-5-methoxycarbonylspiro[pyrrolidine-3,5'-imidazoline]-2',4'-dione (III) and (3S,5S)-stereoisomer. A total of 65 I and II were prepared and 17 I in vitro inhibited 20-100% the carbachol-induced contraction of guinea pig's ileums. Seven formulations, e.g. 200 mg tablets containing 20 mg III, were described.

AN 1994:271177 CAPLUS

DN 120:271177

TI Preparation of optically active amino acid derivatives having fixed conformation and anticonvulsants containing them

IN Sawanishi, Hiroyuki; Myamoto, Kenichi; Tanaka, Kenichi; Suzuki, Koichi

PA Tsumura & Co, Japan

SO Jpn. Kokai Tokkyo Koho, 40 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI JP 05213957	A2	19930824	JP 1992-56058	19920207
PRAI JP 1992-56058		19920207		

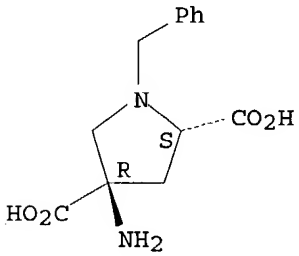
OS MARPAT 120:271177

IT **154342-50-4P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as anticonvulsant)

RN 154342-50-4 CAPLUS

CN 2,4-Pyrrolidinedicarboxylic acid, 4-amino-1-(phenylmethyl)-, monohydrate, (2S-trans)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



● H_2O